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THE ESTIVO-AUTUMNAL

(*REMITTENT*)

MALARIAL FEVERS

BY

CHARLES F. CRAIG, M. D. (Yale)

Acting Assistant Surgeon U. S. Army; Pathologist and Bacteriologist to the U. S. Army
General Hospital, Presidio of San Francisco, Cal.; Late Director of the Bacteriological
Laboratories of the Sternberg U. S. A. General Hospital, Chickamauga Park, Ga.,
The Josiah Simpeon U. S. A. General Hospital, Fortress Monroe, Va.,
and the Camp Columbia U. S. A. Hospital, Havana, Cuba;
Member of the American Medical Association, the
American Microscopical Society, etc.

Illustrated by Two Colored Plates and Twenty-one Clinical Charts

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To

GEORGE M. STERNBERG, M.D., LL.D.
SURGEON-GENERAL OF THE UNITED STATES ARMY

This Volume is Dedicated

IN RECOGNITION OF HIS MANY GREAT AND
VALUABLE DISCOVERIES IN BACTERIOLOGY AND
SANITARY SCIENCE, AND AS A TOKEN OF THE
REGARD AND ESTEEM OF THE AUTHOR

PREFACE

THE reason for the preparation of this volume is given in the introduction. It deals with a much-neglected subject in the text-books upon medicine, and one which is of the utmost importance to the profession. It will be noticed that I have not considered the subject of hemoglobinuric fever at all. This is not an oversight on my part, but because I believe that in a work such as this the subject should be confined as much as possible. As the etiology of hemoglobinuric fever is still somewhat in doubt, and as there are many excellent treatises upon it, I have thought it best to ignore it entirely.

My gratitude is due the Surgeon-General of the Army for the opportunities afforded me to study the malarial fevers. To Colonel A. A. Woodhull, Assistant Surgeon-General of the Army, Colonel William C. Forwood, Assistant Surgeon-General, United States Army, and to Major Charles Richard, Surgeon, United States Army, my thanks are due for encouragement and assistance.

I desire to take this opportunity of expressing my appreciation of, and thankfulness for, the uniform support and enthusiasm of Lieutenant-Colonel A. C. Girard, Deputy Surgeon-General of the United States Army, in the scientific study of disease, and the methods of making such study available. Without such coöperation much of this volume could not have been prepared.

I have freely consulted the works of other investigators, and am particularly indebted to Marchiafava and Bignami, Thayer and Hewitson and Manson, for many valuable data and references. I have tried invariably to give credit where it is due.

To my assistant, Dr. Jobling, I am indebted for the preparation of the index. It is the earnest hope of the author that

the studies contained in this volume may be of value to the medical profession and assist in the elucidation of the fevers of tropical and subtropical countries. The constant aim of the author has been to present as simply and accurately as possible the facts connected with the fevers of malarial origin, known as estivo-autumnal, and I would urge upon the profession the importance of thorough study of these fevers which are so prevalent and fatal in the tropics.

CHARLES F. CRAIG.

February 15, 1901.

CONTENTS

	PAGE
INTRODUCTION	1
CHAPTER I	
Definition of Remittent Malarial Fever—Historical—General Remarks	3
CHAPTER II	
Description of the Parasites Causing the Remittent or Estivo-autumnal Malarial Fevers—The Quotidian Estivo-autumnal Parasite—The Malignant Tertian Estivo-autumnal Parasite	15
CHAPTER III	
The Crescentic, Ovoid and Flagellated Forms of the Estivo-autumnal Parasites	24
CHAPTER IV	
The Life-Cycle of the Estivo-autumnal Parasites within the Mosquito	35
CHAPTER V	
Cultivation and Inoculation Experiments—Phagocytosis—Classification	40
CHAPTER VI	
Examination of the Blood—Methods of Staining—The Structure of the Estivo-autumnal Parasites as Revealed by Staining	48
CHAPTER VII	
Etiology—Predisposing Causes, General and Local	58
CHAPTER VIII	
Etiology (continued)—Direct Infection—By Air—By Water—By Inoculation	62
CHAPTER IX	
Transmission by Inoculation, from Man to Man—Incubation—Immunity—Spontaneous Recovery	71

CHAPTER X

- General Pathology of the Estivo-autumnal Malarial Fevers—Changes in the Red Corpuscles—Melanemia—Anemia—The Urine—The Etiology of the Fever 79

CHAPTER XI

- Special Pathology of the Estivo-autumnal Fevers—Acute Infections . . . 91

CHAPTER XII

- Clinical Description of the Estivo-autumnal Malarial Fevers—Classification and Symptomatology of the Tertian and Quotidian Forms—Analysis of Symptoms and Physical Examination—Examination of the Blood 104

CHAPTER XIII

- Clinical Illustrations of the Quotidian and Tertian Forms of the Estivo-autumnal Malarial Fevers 120

CHAPTER XIV

- The Pernicious Forms of the Estivo-autumnal Malarial Fevers 147

CHAPTER XV

- Latent and Masked Estivo-autumnal Malarial Fevers—Subcontinued or Remittent Estivo-autumnal Malarial Fevers—Combined Infections . 159

CHAPTER XVI

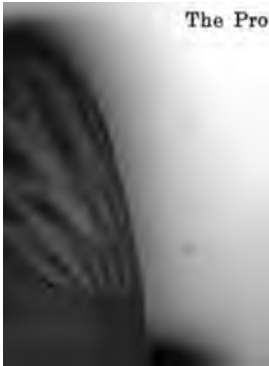
- Complications and Sequelæ of the Estivo-autumnal Malarial Fevers . . 168

CHAPTER XVII

- The Diagnosis and Prognosis of the Estivo-autumnal Malarial Fevers . 185

CHAPTER XVIII

- The Prophylaxis and Treatment of the Estivo-autumnal Malarial Fevers. 199



LIST OF PLATES AND CHARTS

	PAGE
Plate I. The Quotidian and Tertian Estivo-autumnal Parasites . Facing	30
Plate II. Stained Estivo-autumnal Parasites Facing	56
Chart No. 1. Tertian Estivo-autumnal Malarial Fever	109
Chart No. 2. Tertian Estivo-autumnal Malarial Fever	110
Chart No. 3. Tertian Estivo-autumnal Malarial Fever	113
Chart No. 4. Tertian Estivo-autumnal Malarial Fever	114
Chart No. 5. Quotidian Estivo-autumnal Malarial Fever	117
Chart No. 6. Quotidian Estivo-autumnal Malarial Fever	123
Chart No. 7. Quotidian Estivo-autumnal Malarial Fever	124
Chart No. 8. Quotidian Estivo-autumnal Malarial Fever	127
Chart No. 9. Quotidian Estivo-autumnal Malarial Fever	128
Chart No. 10. Quotidian Estivo-autumnal Malarial Fever	133
Chart No. 11. Tertian Estivo-autumnal Malarial Fever	134
Chart No. 12. Tertian Estivo-autumnal Malarial Fever	139
Chart No. 13. Tertian Estivo-autumnal Malarial Fever	140
Chart No. 14. Tertian Estivo-autumnal Malarial Fever	143
Chart No. 15. Tertian Estivo-autumnal Malarial Fever	144
Chart No. 16. Subcontinued Estivo-autumnal Malarial Fever	163
Chart No. 17. Combined Tertian and Tertian Estivo-autumnal Malaria .	164
Chart No. 18. Combined Typhoid and Estivo-autumnal Malarial Fevers .	176, 177
Chart No. 19. Typhoid Fever (Decline)	189
Chart No. 20. Acute Tuberculosis	190
Chart No. 21. Infective Endocarditis (Dock)	193



THE ESTIVO-AUTUMNAL (REMITTENT) MALARIAL FEVERS

INTRODUCTION

IN the following pages it has been the aim of the author to describe minutely certain fevers as yet too little understood by the mass of the medical profession, and which are of the greatest interest, both from a scientific and a practical point of view. The author has approached his task with much hesitation, and only the assurance that, from a long experience with and study of the diseases in question, he may be able to do at least partial justice to them, prompts him to attempt their description.

The work is very largely the result of personal experience gained in the United States military hospitals, and, as such, embodies the conclusions arrived at from nearly three years of investigation and the careful study of hundreds of cases of the estivo-autumnal malarial fevers. A great majority of the cases have been malarias contracted in Cuba and in the Philippines, and it is believed that, whatever the shortcomings of the results obtained may be, the material for study has never been excelled.

From the moment the author began the laboratory investigation of the diseases prevalent in the troops, for the Medical Department of the United States army, he became convinced of the vast importance of a thorough knowledge of the malarial fevers, and especially of the remittent malarial fevers, or, more correctly, the estivo-autumnal fevers, to the practicing physician. At Chickamauga Park, where his first work was done, hundreds of cases of typhoid fever, pure and simple, were diagnosed as remittent malarial fever and treated as such, this being due very largely to the belief that because this camp was located in the south, it must necessarily become infected by malaria. As a matter of fact, there was but very little malarial fever present among the troops at Chickamauga Park, as has been amply

shown by Vaughn, Dock, Reed, Shakespeare, and other investigators. The colossal mistake of diagnosing hundreds of cases of typhoid fever as malaria was really responsible for the terrible epidemic which actually compelled the evacuation of the Park as a camping site. Because the mistake was due largely to ignorance of the nature and methods of diagnosing the remittent malarial fevers, the author has felt it his duty to put upon record his experience with these fevers, together with that of others, in the hope that it may be of assistance to the profession at large.

The charts shown are those of typical cases of the estivo-autumnal fevers, selected to demonstrate the variations in the temperature curve, variations that are often so puzzling that only the microscope can decide with what we have to deal; and throughout the book I have consistently emphasized the infinite importance of the microscopical examination of the blood of all cases of fever, wherever they may develop. There can be no excuse to-day for the failure to diagnose either malarial fever or typhoid, for with the Widal test and the microscope we are armed with all that is necessary for their recognition.

CHAPTER I

DEFINITION OF THE REMITTENT MALARIAL FEVERS (ESTIVO-AUTUMNAL)

GENERAL REMARKS

MALARIAL fevers are of such wide distribution that a proper understanding of their etiology, symptomatology, and treatment is of the utmost importance to the medical profession. In our present advanced knowledge of the subject we know that these fevers are divided into three great classes; viz., the tertian, quartan, and estivo-autumnal malarial fevers, each caused by its own distinct blood parasite, and each presenting distinct and more or less characteristic symptoms.

While the estivo-autumnal, or, as they are more universally known, the remittent forms of malarial fever, are more strictly bounded as regards distribution than are either the tertian or the quartan forms, they are so widely distributed as to make their recognition of the first importance, especially in view of the new fields opened to American colonization by the acquisition of the Philippines, Porto Rico, and Cuba. In all three of these countries the remittent malarial fevers are endemic, especially in Cuba and the Philippines, and will be found, as in all tropical countries, to be one of the greatest obstacles to their colonization. Malaria is a greater foe to civilization in the tropics than is any other one factor, and Koch* justly says: "Malaria is met with everywhere; the officer in his bureau, the traveler in the interior, the soldier upon the march, all must recognize that soon or late they are to become the victims of malaria."

As the tropics are approached, we meet less often with the benign tertian and quartan fever and frequently with the more severe and resistant estivo-autumnal infections, which include also the terrible, pernicious malarial fever and the so-called black-water fever. So varied are the manifestations of this form of malaria that several distinct types have been described clinically.

*"On Recognition, Cure, and Prevention of Tropical Malaria."

but all depend for etiology upon the presence in the blood of those forms of malarial plasmodia known as the estivo-autumnal parasites or plasmodia of Laveran. We may say, then, that estivo-autumnal or remittent malarial fevers are fevers caused by the presence in the blood of definite blood-parasites, and characterized clinically by paroxysms of fever of regular or irregular duration, followed by regular or irregular intermissions or remissions. While this definition is very unsatisfactory, it is probably as descriptive of these protean fevers as any short definition could be, and will, at least, be of service as showing their main points of difference from tertian and quartan malarial fever. The paroxysms and intermissions in the two last-named fevers are regular and definite in their phenomena, but in remittent malarial fevers this is often not so; and while all three are caused by very nearly related blood-parasites, the remittent malarial fevers differ very widely clinically from the tertian or quartan fevers. Koch, in the article just referred to, has striven to prove that the estivo-autumnal fevers are essentially tertian fevers; but to one who has studied these forms of malaria thoroughly, his postulates are unsatisfactory and his array of evidence very far from convincing. I will speak of Koch's theories more fully later, but am convinced that they cannot be supported by facts, and that the estivo-autumnal fevers are far from being as regular in their manifestations as he evidently believes them to be.

HISTORICAL.—The earliest writings upon medicine describe more or less accurately the various types of malarial fevers, and it is probably true that the distinction between the benign tertian fever and the pernicious estivo-autumnal fever was well known to the ancient Greek and Roman physicians. This class of fevers was not known by the term "malarial" until after Torti distinguished them by their yielding to quinine in 1712. It may be said here, in passing, that the quinine test is not always to be relied upon in distinguishing these fevers, especially the estivo-autumnal fevers, and should never be used for diagnostic purposes if a microscopic examination of the blood can be obtained.

Thayer, in his most excellent work, "Lectures on the Malarial Fevers," says: "To-day, however, in the light of our present knowledge, we are able to distinguish the malarial infections from other febrile processes, however similar their clinical manifestations may be, not only by their behavior under treatment with quinine, but also by the presence in the blood of the specific para-

site discovered in 1880 by Laveran." This fact may be said to be one of the greatest advances in modern medicine.

A few of the older writers evidently had some idea of the parasitic nature of malarial fevers, for in 1846 Rasori wrote: "For many years I have held the opinion that the intermittent fevers are produced by parasites, which renew the paroxysm by the act of their reproduction, which recurs more or less rapidly, according to the variety of the species."

The history of the discovery of the malarial parasite covers many years. Mitchell,* in 1849, claimed that the disease was due to spores found in marshy districts. In 1866, Salisbury† made himself famous by announcing the cause of malarial fevers to be certain vegetable cells, which he claimed to have found in the perspiration and urine of patients suffering from the disease. For a time his views were widely accepted. In 1879 Klebs and Tomassi Crudeli‡ found in the soil of malarial districts certain rod-shaped bacteria which, when injected into animals, in pure culture, were claimed by them to produce the symptoms of the disease. Their observations were never confirmed by careful observers, but for some time their views were accepted by a large portion of the scientific world.

In 1880 Laveran,§ a French army surgeon, stationed in Algeria, after careful study of the blood of many cases of malarial fever, announced the discovery of a parasite in the blood which he had no hesitation in claiming to be the veritable cause of the disease. At first his researches attracted little attention, but they were soon confirmed by Richard, Marchiafava and Celli, Golgi, Councilman, Abbott, Sternberg, Osler, Dock, and other observers, and his claim to have discovered the actual cause of malaria abundantly verified.

The reader is referred to Thayer's "Lectures on the Malarial Fevers" for an admirable history of the discovery of the malarial parasite.

Laveran was the first investigator to recognize the relation of the parasites to the disease; but they had undoubtedly been seen before by both Meckel, in 1847, and Virchow, in 1848. The first observer mentioned noticed pigment in the blood obtained from a malarial patient, and that this pigment was contained mostly

*"The Cryptogamous Origin of Malarious and Epidemic Fevers."

†"Am. Jour. Med. Sci.," Jan., 1866.

‡Arch. f. exp. Path. U. Paas. Mak, 1879, x. 1.311.

§Bulletin de l'Académie de Médecine de Paris, séance de 23 Nov., 1880.

in round, ovoid, or spindle-shaped masses of protoplasm. He was probably the first observer to notice the ovoid and crescent forms of the estivo-autumnal organisms.

Laveran noticed and described three forms of the parasite:

a. Oval or crescentic bodies with hyalin protoplasm, containing either a central or polar mass of golden yellow pigment-granules, arranged either in clumps or in a wreath-like arrangement. A faint hyalin bib could sometimes be seen connecting the extremities of the crescent. This form is easily seen to be the crescentic form of the parasite causing estivo-autumnal fever.

b. Small, hyalin, rounded bodies containing a ring of pigment-granules which were motionless. Occasionally one of these bodies was seen with long, thin, hyalin filaments in active motion projecting from its circumference, while the pigment within it was also in rapid motion.

This form is the flagellated form of the estivo-autumnal parasite, which will be described more fully later on.

c. Spherical, slightly granular bodies, with immobile pigment—evidently degenerated forms of the two foregoing classes.

From his observations he concludes that "there exist in the blood of malarial patients parasitic elements which have heretofore been confounded with melaniferous leucocytes; the presence of these parasites in the blood is probably the principal cause of the manifestations of paludism."

Later, Richard* discovered the intracorpuseular hyalin parasites and the segmenting bodies.

Marchiafava and Celli, in 1885, described very carefully the hyalin intracorpuseular parasites, and proposed the term "*plasmodium malarie*" for the parasite. Biologically this term is far from correct and should be abandoned. We are dealing with a parasite conceded by all competent observers to belong to the sporozoa, and having its principal habitat in the blood. The term *hæmaphysa malarie*, proposed by Welch, is more nearly correct, and should be preferred to the term "*plasmodium*."

As, however, in the light of the most recent researches, the biological position of the malarial parasite would still seem to be in doubt, it would be better if in ordinary work the terms "tertian," "quartan," and "estivo-autumnal" malarial parasites were adopted, thus obviating all confusion regarding the exact status of the organism.

*Gaz. med. de Par. 1882, 6 s. 4, 252.

Golgi, in 1885, clearly showed that quartan fever depended upon a specific form of the malarial parasite, which he described and figured. Shortly afterwards he also described the specific parasite causing tertian fever. To him, likewise, we owe the discovery that the malarial paroxysm always coincides with the segmentation or sporulation of a group of parasites. This segmentation, occurring every forty-eight hours, produces tertian fever; while if it occurs every seventy-two hours, quartan fever is the type found. A quotidian fever is caused by the segmentation of two groups of tertian parasites which sporulate on successive days.

Golgi's observations have been confirmed by Grassi, Canalis, Bastianelli, Bignami, Marchiafava, Celli, Mannaberg, Sakarov, Gotye, Sternberg, Osler, Dock, Thayer, Hewetson, and other eminent observers.

DISCOVERY OF THE ESTIVO-AUTUMNAL PARASITES

Golgi, in 1885, was the first to call attention to the probably distinct type of the crescentic and ovoid parasite, and suggested the possibility of its being a new variety of the malarial organism; but to Councilman we owe the first statement of the diagnostic value of these forms. In 1887 he says: "The character of these bodies [the malarial parasite] varies in different forms of the disease. Although they seem in some cases to run into one another, still, in general, we can say that where the plasmodia inside the red corpuscles are seen [large pigmented forms] the patient has intermittent fever, and where the crescentic and elongated masses are found he has either some form of remittent fever or malarial cachexia. . . . We are not only able to diagnose the disease as such, but in most cases the particular form."

Golgi, in 1889, was the first to observe that the small, hyalin, intracellular rings and the crescent and ovoid pigmented bodies were associated with malarial fevers of remittent character with long intervals between the paroxysms. He believed that the ring-forms were the first stage of the crescent and ovoid forms.

The type of fever in which these organisms are found, and which is now known as estivo-autumnal fever, differs very materially from the ordinary intermittent (tertian and quartan) fevers met with in northern latitudes. Under the term estivo-autumnal fever is included the majority of the cases of so-called pernicious

malarial fevers, and their chief characteristics are their irregular paroxysms, protean clinical symptoms, and their greater resistance to quinine. In this class of cases, which are especially prevalent in the malarial districts around Rome where they studied, Marchiafava and Celli, in 1889, discovered and described very minutely the appearance and life-history of the parasites concerned in their etiology. About the same time Canalis published the results of his investigations upon the parasites associated with irregular and remittent malarial fevers, and although his interpretation of some of the phenomena observed differed widely from those of Marchiafava and Celli, the morphological descriptions of the parasites were very similar, and confirmed Golgi's theory of the existence of a separate variety of the malarial parasite causing remittent malarial fever. A brief summary of the investigations of the above-mentioned authors is here given.

Marchiafava's and Celli's observations may be summed up as follows: For some time before an onset of a paroxysm of fever, three forms of the estivo-autumnal parasite may be seen in the blood, i. e., minute round or ring forms, having a small, dark center, composed of pigment or hemoglobin; intracellular, minute, amoeboid, hyalin parasites, containing one to three small pigment-granules, and somewhat larger round bodies having a block of pigment at some portion within them. The red corpuscles containing the parasites were seen to be smaller than the surrounding corpuscles, darker green in color, and crenated, while the hemoglobin was often seen to be retracted from the periphery of the corpuscle for a whole or part of its circumference. Segmenting bodies were very rarely seen in the circulating blood, but were found in large numbers in the internal organs, especially the spleen and the capillaries of the brain. They observed that pigmentation always occurred before the onset of a paroxysm, and that the parasites pursued a developmental cycle of twenty-four hours or less. At the time of the paroxysm, and for some time afterwards, the small amoeboid hyalin parasites, which comprise the new generation, may be seen in the blood. They describe the crescentic organisms and also intervening forms between the intracellular bodies and the crescents. They note the minuteness of the estivo-autumnal parasite as compared with the tertian and quartan forms. They found the crescents in greater number in the spleen, but observed many cases without the formation of crescents. No segmentation of the crescents was

ever noticed, and neither is the development of pigment always to be observed. In those fevers in Rome showing daily paroxysms only the small, hyalin, amœboid, intracellular parasite is observed in the peripheral blood, and only in those cases showing a longer interval between the paroxysms is the parasite with the few pigment-grains to be seen.

Canalis' article is a very elaborate one. He divided the cycle of development into two phases: a rapid cycle, and a slower cycle in which the crescentic forms appear. The rapid cycle he considers to be of about two days' duration, though it may be only twenty-four hours in length. During the first hours the parasites are intracellular, amœboid, hyalin, occupying one-sixth of the red corpuscle, the outer portion of the parasite being clear, while the center appears shaded or greenish, presenting the appearance of a nucleus. The outer portion may be very refractive. The blood-corpuscles which they have invaded are very often smaller than normal and are greenish in color. As the parasite grows it becomes more amœboid, and a few fine particles of reddish brown pigment may be seen within the outer ring-like portion. The parasite gradually grows larger, the ring-like appearance disappears, the amœboid movement ceases, the pigment-granules melt into one small solid block at the center, or one side of the parasite, and a faint radial striation appears, and from six to ten ovoid or round segments are eventually produced. They are much smaller than the segments of tertian or quartan fever. The containing corpuscle may be entirely disintegrated or may appear as a dim, shadowy sphere surrounding the segments. Segmenting bodies are very rarely seen in the circulating blood, but free pigment and pigmented leucocytes are common.

The second, or slow, cycle, in which crescents develop, may occur in connection with the rapid cycle, or where the course of the disease has been interfered with by some drug, especially quinine. Canalis always found that crescents were not developed until some time after the onset of the fever, generally not until fifteen days had elapsed. The small, intracellular, amœboid forms were observed to become oval in shape, while the pigment collected toward the center; a crescentic form was gradually acquired; the red corpuscle disappeared, and the now fully formed crescent was set free in the blood. He observed the double outline of the crescent, and considered that it was due to an enveloping

membrane. The crescents were afterwards observed to acquire an oval form and finally become perfectly round. In the crescentic and ovoid forms the pigment was always motionless, but in the round form it often became very mobile, and was arranged in a perfect circle. He describes a process of sporulation as occurring at this time from the second bodies. The segments are round or oval. He distinguishes this process from a degenerative process which often occurs, as follows: "In this degenerative process one meets with bodies which have lost their yellowish or ashy color and have become clearer, sometimes refractive, with a double contour much more marked than that of the ordinary parasite, while their substance is transformed into a mass of round or irregular bodies of various sizes and with a single contour. If one continues the microscopic examination of one of these parasites during the course of several minutes, he may sometimes see that two or three of these spherules become united with a single body, thus forming irregular masses which, continuing the process of fusion, finally give to the parasite a homogeneous aspect without trace of spherules.

"The pigment is sometimes arranged as a central crown, sometimes scattered irregularly at an extremity or at one side of the body. The points which distinguish this process from that of sporulation are: the refractiveness of the degenerating body; the irregularity in size of the spherules; the absence in these spherules of a more opaque central area; their fusion into irregular bodies and finally into an amorphous mass."

He also observed the development of flagellate bodies from the round bodies, and of them he says: "They represent, assuredly, one of the last stages in the development of the parasite, for I have never seen them appear in the blood before the formation of the round bodies."

Canalis considered the length of this cycle to vary, the period from the amoeboid stage to the crescentic lasting from three to four days, the development of the round bodies taking a day longer.

In this truly admirable paper it is unfortunate that the author committed himself to the sporulation theory of the crescents, for in the light of our present knowledge such a theory is untenable, and no modern investigator has ever observed the sporulation of a crescentic organism.

That a distinct type of parasite is always associated with the estivo-autumnal fevers has been confirmed by every intelligent

investigator, and Bignami, Sanfelice, Phlen, Mannaberg, Dock, Thayer, Hewetson, and the author have confirmed much that appeared in the articles of Marchiafava, Celli, and Canalis; but there is yet much diversity of opinion as to the classification of the forms observed.

Marchiafava and Bignami have very thoroughly investigated the parasites occurring in the estivo-autumnal fevers, and, as the result of their studies, have separated these parasites into two varieties, one causing a paroxysm every twenty-four hours, the other every forty-eight hours, approximately, and which they have termed the quotidian and malignant tertian estivo-autumnal organisms. The fever caused by the quotidian parasite may be regular and resemble the ordinary double tertian paroxysm, but more often the temperature curve shows evidence of anticipation or retardation, being irregular, and the symptoms vary much in their severity. A continuous or slightly remittent fever is not unusual. The quotidian parasite, as described by them, is generally seen as a very small, amœboid, hyalin, ringlike, intracorpuscular body, in the circulating blood, which prior to segmentation develops a small number of minute pigment-granules. Segmentation generally occurs within the red corpuscle, and almost always in the internal organs, especially in the spleen. The rings are very pale and often require very careful search before they are discovered, are actively amœboid, and never exceed one-third of the corpuscle in size. The infected corpuscle has a greenish, brassy color, is often shrunken, and the hemoglobin retracted. After some days crescentic and ovoid bodies appear.

Marchiafava and Bignami's malignant tertian parasite produces a febrile paroxysm lasting from twenty-four to forty hours, and often the temperature curve shows such variations, caused by the anticipation and conjunction of paroxysms, as to present a continual fever. According to them the febrile curve presents, in the majority of cases, the following characteristic points: rapid and sudden rise, a stationary stage, with slight remissions, a slight pseudocrisis, a precritical rise, marked often by the highest temperature, and at last a sharp crisis during which the temperature often falls far below normal. Very often the temperature curve is very irregular, due, as quoted by Thayer and Hewetson,* to the following influences:

* "Malarial Fevers of Baltimore," Johns Hopkins Hospital Reports, Vol. V.

1. By modification of the curve in the individual paroxysms.
2. By modification in the succession of the paroxysms.
 - A. The important modifications of the curve are the following:
 - a. The lack of a sharp initial elevation, so that the curve rises in a progressive and continuous manner.
 - b. The exaggeration of the pseudocrisis so that the attack tends to lose its individuality.
 - c. The prolongation of the paroxysm, which is usually associated with an exaggeration of the thermic oscillations during the fastigium.
 - d. The lack of a sharp precritical elevation.
 - B. The modification in the succession of the paroxysms may be:
 - a. The anticipation of the paroxysms, which can occur in the mild as well as the severe forms.
 - b. The retardation, which can occur also in the grave infections.
 - c. The prolongation of the paroxysms, by which apyrexia is made incomplete.
 - d. The presence of slight oscillations in the temperature during the period which ought to be one of apyrexia.
 - e. The reduplication of the attacks.

Quinine will also cause important modifications in the temperature curve.

The malignant tertian parasite, as described by these authors, resembles the quotidian very closely, but is larger and presents a greater amount of pigment within its protoplasm. It is often one-half the size of the red blood-corpuscle. Like the quotidian, segmentation takes place mostly within the vessels of the internal organs. The infected corpuscles are almost invariably shrunken, dark green in color, and often crenated and degenerated. Crescentic and ovoid forms appear after a few days.

The difference between the quotidian and malignant tertian estivo-autumnal parasites, as given by Marchiafava and Bignami, and tabulated by Thayer and Hewetson,* are as follows:

1. The length of the cycle of development, which in the quotidian parasite lasts about twenty-four hours, and often

*"The Malarial Fevers of Baltimore," Johns Hopkins Hospital Reports, Vol. V.

occurs without the development of pigment, while in the tertian it lasts forty-eight hours, and is always associated with pigmentation.

2. The size of the amœba; in the same relative stage of development the amœba of tertian fever is generally larger and of a more transparent appearance.
3. The movements, which in the tertian parasite are retained for a longer time by the larger pigmented forms than in the quotidian parasite; they are also more active in the tertian organism.
4. The length of the amœboid unpigmented stage, which, in the tertian body, may last more than twenty-four hours.
5. The time elapsing after the beginning of the new paroxysm, before the appearance of the new generation of parasites, which, in the tertian fever amounts to several hours, considerably longer than with the quotidian type.

Mannaberg distinguishes three varieties of the estivo-autumnal parasite—an unpigmented quotidian, a pigmented quotidian and the malignant tertian parasites. Grassi and Feletti also describe the pigmented and unpigmented quotidian parasites. In 1893 Golgi published his researches concerning the parasite of estivo-autumnal fever, in which he vigorously combated the existence of more than one variety of the estivo-autumnal organism, and stated that the forms found in the circulating blood were chiefly accidental, the infection being present almost entirely within the internal organs.

Gautier, Korolko, Zieman, Dock, Thayer, and most of the American authorities, accept only one variety of the estivo-autumnal parasite. My own views upon this subject will be given in detail in the next chapter, but a large number of observations have convinced me that two varieties of the estivo-autumnal parasite do exist, and can be demonstrated where the clinical material is available. Wilson and Ashton* say regarding the estivo-autumnal parasite: "Its development is accompanied with more irregularity than that which attends the other varieties of parasites, and while clinically it may be possible in the milder instances of infection to recognize certain types, such as quotidian and tertian, the type is so confused as to render its analysis almost impossible." This statement is too radical,

*"Encyclopedia of Medicine," Sajous, p. 465.

for study of this class of malaria will convince any one that the quotidian and tertian estivo-autumnal fevers do exist, can be easily recognized if quinine is withheld, and that each is caused by its own characteristic parasite.

Quite recently Sternberg and Munson have, in their writings, classed the estivo-autumnal parasites in two divisions, the quotidian and tertian, thus following Marchiafava and Bignami's classification. Thorough study of the blood and the clinical manifestations in the estivo-autumnal malarial fevers has not received the attention which the importance of the subject deserves, especially in this country, due very largely to the comparative rarity of these types of malarial fever, but, as stated before, research along this line will prove conclusively the truth of Marchiafava and Bignami's deductions regarding the estivo-autumnal malarial fevers.*

*"Popular Science Monthly," Feb., 1901; "Military Hygiene," 1901.

CHAPTER II

THE DESCRIPTION OF THE PARASITES CAUSING THE REMITTENT (ESTIVO-AUTUMNAL) MALARIAL FEVERS—THE QUOTIDIAN ESTIVO-AUTUMNAL PARASITE—THE MALIGNANT TERTIAN ESTIVO-AUTUMNAL PARASITE

BEFORE describing the parasites concerned in the etiology of this form of malaria, a few words regarding the course of the temperature curves is in place. While we may, and often do, have, in patients who have been taking quinine, the most irregular and uncharacteristic temperature-curve pictures, occurring with remittent malarial fever, still, in the tropics, and in uncomplicated cases in this country, the temperature curve in the great majority of cases conforms to one of two types, i. e., a quotidian or tertian paroxysm, with intermissions. In the quotidian estivo-autumnal fever the temperature curve resembles very closely that of an ordinary double tertian, there being a sharp daily rise followed by a remission or, generally, an intermission. This type of estivo-autumnal fever embraces a large portion of those cases showing pernicious symptoms, and is much more rare than is the tertian type.

The tertian type of remittent malarial fever, as observed by me, is marked by a very characteristic temperature curve, is the most common form of the disease, and corresponds to Marchiafava and Bignami's malignant tertian fever. Many observers, especially Koch, consider all cases of estivo-autumnal fever to belong to this type; and while this may be true of the cases studied by them, all cases of the disease can by no means be so classified. The temperature curve exhibited by this form of the disease may be briefly analyzed as follows: A rapid and sudden rise, a stage with slight remissions, a pseudo-crisis, a precritical rise, in which the temperature goes above the highest point previously reached, and, lastly, the true crisis, in which the temperature falls rapidly below normal. We may have great irregularities and variations in both these forms, due to causes which influence the temperature in any febrile disease; but the majority of cases will be found to conform to

these types. A great source of fallacy in our study of malaria lies in the difficulty of getting the cases before quinine has been administered; the administration of this drug interferes very markedly with the true course of the temperature curve, and is the chief reason why most observers in this country have been unable to demonstrate the existence of quotidian and tertian remittent malarial fever, in studying the malarial fevers so common among our soldiers returning from Cuba. If quinine is stopped in such cases, however, the fever is almost sure to recur soon, and will, in time, exhibit the characteristic curve. The study of hundreds of cases of malaria in soldiers returning from Cuba and the Philippines, and of a large number of cases in Cuba, has convinced me of the truth of the facts stated, and though I realize that many authorities may differ with me, I can only say to such: Study the disease uncomplicated by quinine and in its native habitat, as in Cuba, and there will remain no doubt, even in the mind of the most skeptical, of the truth of the observations noted in this chapter.

It should not be forgotten that in many instances, especially in the tropics, a combined infection may be present of both varieties of the parasite, and of course both may be found in the blood in different stages of development. Such cases have been largely to blame for the confusion which has existed regarding these parasites.

In ordinary tertian and quartan malarial fever we have no difficulty in following the various stages of the development of the parasites in the circulating blood; but in the estivo-autumnal fevers this is not so, as only the hyalin and slightly pigmented bodies are present in the circulating blood, and in order to study the larger pigmented and segmenting forms it is necessary to obtain blood by puncturing the spleen. This is a dangerous and generally unnecessary procedure, so far as diagnosis is concerned, for the forms found in the circulating blood are sufficient for such purposes; but for the scientific study of the parasites the procedure is necessary, and if due precautions are used, the danger is very slight.

The remittent or estivo-autumnal malarial fevers, like tertian and quartan malarial fever, are due to blood parasites, having two life-cycles. One cycle, that in which we are most interested, is completed in man; the other, hardly less interesting and probably more important from a prophylactic standpoint, is

completed in insects, limited, so far as our present knowledge extends, to mosquitoes.

In man the development and growth of the parasites causes the complex symptom-picture known as malaria, and after the parasite has reached a certain stage of development in man it is taken up by the mosquito, in whose intestine it undergoes certain other changes, and finally becomes lodged in the venomo-salivary glands of the insect, from which it again reaches man when the insect bites.

It is my purpose in this chapter to describe certain stages in the life-cycle of the estivo-autumnal parasites in the human body, reserving for the next chapter the consideration of the special forms of the parasites having to do with the life-cycle in the mosquito.

In the description of the estivo-autumnal parasites I shall divide the subject as follows: (1) The quotidian estivo-autumnal parasite—the hyalin body, the pigmented body, the segmenting body; (2) the malignant tertian estivo-autumnal parasite—the hyalin body, the pigmented body, the segmenting body.

THE QUOTIDIAN ESTIVO-AUTUMNAL PARASITE.—*The Hyalin Body*.—This form of the malarial parasite completes its development in twenty-four hours, as a rule. The parasite appears first as a very minute (.5 to 1 μ in diameter) ring-shaped or round hyalin body, actively amœboid, within the red blood-corpuscle. The outline of the organism is very indistinct and, were it not for its active amœboid movement, it would be very easily overlooked. The ring form is usually perfectly circular when at rest, the center appearing of the same color as the corpuscle within which it lies; the organism is not very refractive and its outline is not sharply cut. When in motion it often appears triangular in shape, the movement consisting of a rapid, wavy motion of its border and the shooting out of minute protoplasmic prolongations which are retracted almost as quickly as thrown out. The motion is not sluggish, but very rapid. Sometimes the ring form is lost, the organism becoming a pale hyalin disc. The movement is very erratic, and there are long periods of repose during which the ring form is retained. The organism is very small and never grows to occupy more than one-sixth of the corpuscle. The corpuscle containing the parasite is smaller than those surrounding it, presents a shrunken, wrinkled appearance, and is dark green in color.

Often two or more parasites are seen within one corpuscle. There is no signet-ring appearance, so common in the malignant tertian parasite. It is in this form of estivo-autumnal fever that the red corpuscles are most rapidly destroyed, and in pernicious cases almost every corpuscle in a microscopic field will be seen to contain a parasite. While the amœboid movement is not as constant as in the tertian parasite, it is more rapid and has to be watched for carefully.

The features to be noticed in the hyalin stage of the quotidian estivo-autumnal parasite are: its minute size (never more than one-sixth the size of the red corpuscle), its indistinct outline and the rapidity of its movement. This stage is seen in the circulating blood best during or immediately after a paroxysm.

The Pigmented Stage.—Just prior to pigmentation the parasite becomes a little larger, loses its ring form, becomes more refractive and sharply defined, much more so than is the malignant tertian parasite. In this parasite I have never observed a pigmented ring, the rule being that before pigmentation the ring form is lost. The pigment appears as a single, or at most two, granules, either in the center or at one side of the parasite, and is always perfectly motionless. Sometimes the pigment appears as a rather coarse, irregular block situated in the center of the parasite, and I have considered such an appearance as denoting the approach of a segmentation. The infected corpuscle is always shrunken, greenish in color, and often crenated. Often, also, the hemoglobin seems to have retracted around the parasite. At this stage it is never more than one-fourth the size of the corpuscle. The chief points of interest at this stage are: loss of ring form before pigmentation, lack of motion of pigment-granules, changes in the infected corpuscle. Pigmented forms are by no means rare in the circulating blood, and are most numerous just before or during a paroxysm. The pigment is dark red or black in color. Amœboid motion is lost.

The Segmenting Body.—This stage is rarely observed in the circulating blood. I have only observed segmenting bodies three times in over one hundred cases of quotidian estivo-autumnal fever, and only in the pernicious type. In blood from the spleen, or in smears from that organ, taken after death, segmenting forms are common. In the parasite which has become pigmented, little change is noticed prior to segmentation, save that the pigment is collected in a solid block at the center of the

organism, while its protoplasm has become very finely granular in appearance. The pigment may be situated at one side, and the parasite is always round or oval in shape. As segmentation commences, faint radial striations can be detected starting from the center, and soon the organism breaks up into from six to eight minute round or oval segments. "Marguerite" forms are rare, irregular segmenting forms being the rule. A peculiarity of the process of segmentation in this form of the parasite is that it occurs generally inside of the red corpuscle before its entire destruction. In all the cases in which I have observed segmenting forms in the circulating blood, segmentation has occurred within the corpuscles, and this is one of the characteristic phenomena observed in the life-cycle of the quotidian estivo-autumnal parasite. The segmenting bodies are most common just before or during a paroxysm.

The chief points of interest at this stage are: The granular appearance of the parasite, the occurrence of segmentation within the red corpuscles, and the small number of segments.

Presence of the Quotidian Parasites in the Blood in Relation to the Attack.—During the acme of the elevation of the temperature and the sweating stage the small amœboid parasites are found in the blood within the red corpuscles. The number of infected corpuscles varies greatly, some cases showing only one or two in the whole specimen, while in others every microscopic field will show several. At this stage the parasites are always unpigmented, and often show no amœboid motion for longer or shorter periods of time.

During the afebrile stage the blood will show, besides the ring forms, a few or many, as the case may be, small pigmented bodies, generally circular in shape and containing one or two small pigment dots.

Just before the onset of the paroxysm, and often during the initial rise of the fever, larger pigmented forms are present, the pigment generally being collected near the center of the parasite, while the infected corpuscles are very brassy in appearance. The segmenting forms, as has been noted, are only very rarely seen in the circulating blood. In typical cases of quotidian estivo-autumnal fever, or where there is infection with more than one group of parasites, the presence of the various forms in the blood becomes irregular, and hyalin and pigmented forms may be observed at almost any time; but there will always be found a



greater number of forms which correspond to the stage of the disease, as shown by the clinical chart. Often in a double infection only a very few parasites belonging to one group will be seen, while there are multitudes belonging to the other group present, and it will invariably be found that it is the most numerous group which is responsible for the clinical symptoms.

It is this form of the estivo-autumnal parasites which is most often found in the pernicious forms of the disease resulting fatally, but it is rare when compared to the form to be described next. The great majority of the cases of remittent malaria occurring in our soldiers in Cuba and, as far as I have observed, in those returning from the Philippines, were caused by the malignant tertian form of the parasite; but now and again, a pure case of quotidian fever would present itself, and the characteristic parasite could always be demonstrated when quinine had not been administered.

THE MALIGNANT TERTIAN ESTIVO-AUTUMNAL PARASITE.—This is the most common parasite associated with estivo-autumnal fever, and is the one which has been most studied and is best known. The reason for this is not hard to find. The majority of cases of estivo-autumnal fever, especially in this country, are due to this parasite, and even in those cases in which the quotidian parasite has occurred, it has probably been in conjunction with the tertian, as those who read the varied descriptions of the parasite of estivo-autumnal fever will be forced to admit.

The Hyalin Stage.—Like the quotidian parasite, the first stage in the development of the tertian organism consists of a round hyalin ring or disk, but several important differences are to be noted, i. e., the ring is larger, being from one-third to one-quarter the size of the corpuscle; it is irregular, presenting an enlargement at some portion of its circumference, giving it the so-called signet-ring appearance; it is highly refractive and is sharply cut, looking as though it had been punched out of the corpuscle; its protoplasm is clear and homogeneous: its amœboid movements are slow and sluggish as compared with the quotidian parasite. The ring form is often lost, a clear hyalin disk resulting. The changes in outline are very marked, and it is much easier recognized than is the quotidian parasite. Only very rarely does more than one organism invade a single corpuscle, as is common in the quotidian form. The infected corpuscle is greenish, and smaller, but is not so markedly affected as in the quotidian.

The Pigmented Stage.—In the course of twenty to twenty-four hours, during which time the hyalin body has been amœboid, a few fine pigment-granules make their appearance within the ring, generally in the enlarged area at one portion of its circumference, thus giving the organism a still greater resemblance to a signet-ring; the amœboid movement continues, and the pigment-granules themselves are often seen to be in rapid vibratory motion. The pigment is reddish in color, and is present in larger amount than in the quotidian parasite. The organism gradually loses its ring form and becomes larger, sometimes occupying one-half of the corpuscle; at the same time, it becomes more clearly defined, its protoplasm more refractive and faintly granular in appearance. The amœboid motion still continues, though very sluggishly, and the pigment tends to collect in a solid block, which has a marked vibratory movement. The pigmented form is somewhat rare in the circulating blood, but blood from the spleen will show immense numbers of them. The chief points of interest are: appearance of pigment in the ring form, sharply cut outline and granular protoplasm, mobility of the pigment-granules, and larger size.

The Segmenting Stage.—In about forty-eight hours the parasite has grown to be one-half to two-thirds as large as the red corpuscle, the pigment has become motionless and collected in a block near the center, and distinct radial striations are visible. The segments are larger than those of the quotidian organism, are more oval in shape, and number from ten to fifteen or more. The segmentation usually occurs outside of the corpuscle. I have observed segmenting bodies but once in the circulation. The parasite is very refractive, sharply outlined, and the protoplasm is granular.

One of the most characteristic features of the malignant tertian parasite, after the ring form has been lost, is the peculiarly refractive, finely granular appearance of its protoplasm, resembling very closely that of the crescents. The pigment is also in finer particles, but there are more of them.

Presence of the Tertian Estivo-Autumnal Parasite in the Blood in Relation to the Attack.—During the acme of the temperature and until the afebrile stage is reached, the small non-pigmented hyalin, amœboid ring forms or disks are found in the circulating blood, with occasionally, at the acme of the fever, a larger pigmented body.

During the afebrile stage, the ring forms gradually develop pigment, and the nearer the time of onset of the paroxysm approaches, the larger and more numerous do the pigmented forms become. Just before the paroxysm, the blood will probably show a few pigmented forms, occupying from one-half to two-thirds of the corpuscle, which is brassy in color, the hemoglobin often being retracted around the parasite. The pigment in such parasites is usually collected at the center, and is immobile. Often at the commencement of a paroxysm the blood from the ear or finger will show no parasites and but a few pigmented leucocytes. However, if the blood be examined when the attack is at its height, i. e., when the fever is highest, numerous ring forms will be found. Although segmenting forms can be readily found at the onset of a paroxysm in blood from the spleen, they very rarely occur in the blood taken from the ear or finger. Very many cases, both of quotidian and tertian estivo-autumnal fever, will be found which show at most but very few pigmented parasites in the peripheral blood, and often, if the blood be examined but once, none at all will be found, though a few ring forms can always be found, provided they are looked for at the proper time, and the examination persisted in. Nowhere does one discover the fact that "patience is a virtue" more quickly than in examining the blood of cases of estivo-autumnal fever. Often a half hour will be spent before a parasite is found, though in the majority of cases so long a search is not necessary. In estivo-autumnal fever, the parasites are always most numerous during the apyrexial stage; but there are often seen mild cases of the disease in which, only after tedious and repeated examinations of the blood, will the parasites be found. In such cases pigmented leucocytes are almost always present, and it is justifiable to make the diagnosis of malaria from them alone.

The summary given may serve to make more clear the differences between the quotidian and malignant tertian estivo-autumnal parasites.

I would say that from my observations of the estivo-autumnal malarial fevers in this country and Cuba, comprising both microscopical and clinical study under exceptional conditions as regards opportunity and material, I am forced by the logic of facts to confirm Marchiafava and Bignami's conclusion regarding this type of malarial fever. There undoubtedly exist two varieties, at least, of the malarial parasite giving rise to these

fevers: one having a cycle of development of twenty-four hours and giving rise, in uncomplicated cases, to a fever having quotidian paroxysms; the other having a life-cycle of forty-eight hours, and giving rise to a fever with tertian paroxysms, in which the temperature curve is peculiar and characteristic.

Stage of Development.		Quotidian.	Malignant Tertian.
The hyalin body.	Size.....	Minute $\frac{1}{4}$ of corpuscle.	Larger $\frac{1}{4}$ to $\frac{1}{2}$ of corpuscle.
	Shape.....	Ring or perfectly round.	Signet-ring shape.
	Motion.....	Very active.	Sluggish.
	Outline....	Indistinct.	Clear cut and refractive.
	Blood-corpuscle....	Very dark green wrinkled. Crenated.	Light green, less wrinkled.
	Number....	More than one parasite in a corpuscle, common.	Very seldom more than one parasite in a corpuscle.
The pigmented body.	Size.....	$\frac{1}{4}$ size of corpuscle.	$\frac{1}{4}$ size of corpuscle.
	Shape.....	Round. Loses ring form before pigmentation.	Ring form becomes pigmented, afterwards the parasite is round.
	Motion.....	Amœboid motion is lost.	Amœboid motion continues. Is sluggish.
	Outline....	More sharply defined.	Very sharply defined, and refractive. The protoplasm firmly granular.
	Pigment...	One or two coarse granules, perfectly motionless.	Several minute grains, having a rapid vibratory motion.
	Number....	May be more than one in a corpuscle.	Never more than one in a corpuscle.
The segmenting body.	Corpuscle..	Very green in color, often crenated.	Lighter in color, seldom crenated.
	Place of segmentation.	Within the red blood-corpuscles, as a rule.	Outside the red blood-corpuscles, as a rule.
The crescent phase.	Number of segments.	Six to eight.	Ten to fifteen, or more.
		Crescents small and plump, containing small amount of pigment. Always present double outline.	Crescents long, narrow, deeply pigmented. Double outline less common.
Cycle of development.		Twenty-four hours.	Forty-eight hours.

CHAPTER III

THE CRESCENTIC, OVOID AND FLAGELLATED FORMS OF THE ESTIVO-AUTUMNAL PARASITES*

So far I have considered the forms of the estivo-autumnal parasites which belong properly to the life-cycle of the organisms within the human body. The crescentic, ovoid and flagellated forms now to be described are those phases of the parasite which, as Marchiafava well says: "begin in man the life-cycle which is completed in the mosquito." In the next chapter I shall consider fully the mosquito cycle of the estivo-autumnal parasites, together with the experimental data which has accumulated concerning this most interesting and important etiological question.

Time of Occurrence of Crescents and Ovoids.—After infection with the estivo-autumnal parasites has persisted for a certain length of time, peculiar endoglobular bodies appear in the circulating blood, which, from their morphological peculiarities, are known as crescentic and ovoid bodies. As to the exact time in which the crescents appear authorities differ somewhat. Canalis† says that he has never but once seen crescentic bodies in the blood before the fifteenth day of the disease, but most other authorities claim that they occur after the disease has persisted a week or more. From my own observations I believe that they may occur in the peripheral blood as early as the seventh day of the disease, and if splenic blood be examined, much earlier, even by the fourth or fifth day. Crescents occur only in the blood of patients suffering from the estivo-autumnal fevers.

DESCRIPTION OF THE CRESCENTS.—These forms of the estivo-autumnal parasite, as their name implies, are crescentic in shape, being smaller at their extremities than in the middle. They are longer than the diameter of the blood-corpuscle, and are always endo-globular. All stages in the development of the

* A portion of this chapter is taken from an article by the author in the "New York Medical Journal" for Dec. 23, 1899.

† Canalis, "Studi sull' infezione malarica. Siomale medici del esercito e della marina." Dec., 1899, p. 1329.

crescent within the blood-cell have been observed, and will be considered later. When fully developed, the crescents are beautifully typical in shape, having a very refractive, more or less finely granular protoplasm, and containing within them, generally at the center, but often at one or the other pole, a clump of pigment which is usually in the form of slender rods or round dots. This pigment is dark in color. In the young crescents the pigment is distributed throughout the protoplasm but becomes collected at the center or one end as the crescent matures. The border of the crescent is sharply cut, being represented by a single or double line which has a peculiar greenish color. In most crescents, when fully grown, careful examination will show a dim line upon the concave side of the crescent connecting the two horns. Often this "bib," as it is called, has a distinct yellowish green tinge, showing it to be, as is the case, the remains of the red blood-corpuscle in which the crescent was developed. The greenish tinge of the border of the crescents is due to the hemoglobin of the red cell which has retracted about it, and formed an enveloping membrane. The finer structure of the crescent will be considered in the description of the staining reaction of the parasites.

Distinction Between the Crescents of the Tertian and Quotidian Estivo-Autumnal Parasites.—Crescents are developed in the life-cycle of both varieties of the estivo-autumnal parasites, and their morphology differs in a few particulars. The tertian estivo-autumnal crescent is large, very slender, with pointed extremities, very refractive and seldom shows a double outline. Its protoplasm is finely granular, and the pigment large in amount and in the form of slender rods.

The quotidian estivo-autumnal crescent is much shorter and plumper than is the tertian, sometimes being very small. Its extremities are never pointed, but instead are rounded, and it always presents a distinct double outline. The protoplasm is less granular, and the enclosed pigment is smaller in amount and in the form of dots.

As a rule, the pigment within both forms of crescents is immotile, but I have seen sluggish motility in the pigment in a few instances.

Crescents undergo certain degenerative changes, the most common of which is *vacuolization*. Such crescents become altered in shape, less refractive, and throughout their protoplasm may be

observed small vacuoles. Another degenerative change is less common and consists of the breaking up of the crescent into small fragments, known as *fragmentation*. At one time this was considered a reproductive phenomena, but in the light of our present knowledge it is undoubtedly degenerative. Along with the crescents in the blood may be seen sometimes forms known as *fusiform bodies*, and they differ from the crescents only in that they are not crescentic in shape. The ends of the spindle are generally pointed, and the contained pigment, which is motionless, is often distributed throughout the protoplasm. Marchiafava claims that these forms are most often found in pernicious cases of the disease.

THE OVOID AND ROUND, OR PREFLAGELLATE BODIES.—Occurring in the blood with the crescents are often found ovoid or round bodies. These bodies are developed from the crescents, and this development can often be followed in the blood, a crescent changing into an ovoid body and that into a round or preflagellate organism. The ovoid bodies are really intracellular, and become extracellular prior to flagellation.

THE FLAGELLATE BODIES.—Ever since the discovery of the plasmodium of malaria by Laveran the nature and significance of the flagellated organism have constituted a mooted question. Held by some authorities to be of a degenerative nature, and by others as evidences of vital activity, the flagella have been closely studied, and a considerable literature has been accumulated concerning them. In the light of recent research, it can no longer be doubted that the evolution of the flagellated organism is a vital and most important phase in the life-history of the plasmodium, and that the theory that it is a degenerative body must be abandoned.

As a result of studies of the flagellated parasites, I believe that in the blood of patients suffering from the estivo-autumnal fevers there occur two forms of flagellated organisms: one a true flagellated parasite, the other a pseudo-flagellated parasite. To the first I have, for convenience, applied the term "active flagellated plasmodium;" to the latter, "passive flagellated plasmodium."

Method of Obtaining Flagellated Organisms.—It is a well-known fact that under ordinary circumstances flagellated plasmodia do not appear in a specimen of blood until some time after it has been removed from the body, generally from fifteen to twenty minutes. This rule has exceptions, however, for I have seen flagellated organisms in a blood specimen which had been

removed only ten minutes from the circulation; this is a rare exception and even in specimens long removed from the body flagellated parasites are not always found. I have found the following method of obtaining these bodies at once simple and effective. The finger or ear is carefully cleansed with alcohol, as are also the slides and cover-glasses. A small elastic band is now placed around the finger, or, if the lobe of the ear is used, it is compressed by an assistant. The puncture is made with a sterile needle or lancet and the first drop of blood wiped away. A second drop is now squeezed out and allowed to remain exposed to the air until the slide is breathed gently upon by the operator, when the tip of the drop of blood is gently pressed upon the surface of the slide which has been breathed upon. The cover-glass is then immediately placed over it, and the preparation is ready to examine. The slight exposure to the air, and the small amount of moisture upon the slide caused by breathing upon it, seems to hasten exflagellation, for specimens so prepared almost invariably contain flagellated bodies. In specimens prepared in this way I have noticed as many as twenty flagellated bodies in one preparation, and have often observed two in a single field. In my observations upon the bodies in question I have used this method exclusively, and have never experienced any difficulty whatever in finding material,—i. e., flagellated bodies for study. This method was first described, in part, by Manson.

Description of Flagellated Forms.—As I have stated, in cases of estivo-autumnal fever, I have almost invariably observed two seemingly distinct forms of the flagellated bodies. By this statement it is not meant that every case of estivo-autumnal fever examined showed these forms, but that the cases showing flagellated bodies presented them.

Description of the Active Flagellated Plasmodium (Estivo-Autumnal Fever).—In examining a specimen of blood from estivo-autumnal fever, a number, sometimes only one or two, of rather large, almost circular, bodies are noted, with the characteristic pigment distributed over the surface and in very active motion. The motion is aptly described as dancing, is very much more rapid than that ordinarily present in the parasite, and at once attracts attention for that reason. Quite often, however, these swollen bodies will be seen, the pigment when first noticed being immotile, but suddenly developing very active motility while

being observed. When the pigment is immotile it seems to be collected in small blotches or spots within the protoplasm of the parasite, but when in motion it is distributed quite evenly throughout the protoplasm. Besides the very active motion of the pigment-granules, if the edge of the parasite be carefully watched, it will be seen that it also is in motion, undulating and protruding, as though, as Richard said, something contained within the parasite were trying to escape. In a variable length of time—from five minutes to half an hour or more—the pigment will be seen to collect more centrally, the motility being somewhat lessened, and instantly, like an explosion, there appear at certain portions of the edge of the parasite long, thin, colorless, actively moving filaments, which undulate rapidly, lashing about among the red corpuscles, to which they impart sometimes a peculiar spinning motion. The filaments may number from one to five, and are usually long and thin, having a slightly clubbed extremity. The junction of the flagellum with the parasite is not visible, it seeming to be continuous with the periphery of the organism.

Besides the clubbed extremity, the flagella sometimes show small nodular swellings in their course, and also a few grains of pigment, which may be distributed along them or collected at the extremity. They generally measure about two or three times the diameter of the parasite from which they spring, but sometimes may be even longer. There also occur shorter, stouter forms, having a more sluggish, serpentine motion.

There may now occur one of several things: either the flagella may break loose from the parent parasite, they may become gradually motionless and disappear, they may fold themselves around the parasite, which shrinks and degenerates, or the parasite may itself fragment and the flagella degenerate and disappear.

In the first case, after the flagellum has lashed about among the blood-corpuscles for a variable length of time, seemingly trying to free itself from the mother parasite, it at last succeeds, and swims off in a serpentine manner among the red corpuscles. In some cases the flagellum tugs very vigorously in its efforts to free itself, actually pulling the mother parasite about but, of course, for only a minute distance. After it has become free it may exhibit motion for a long time, even an hour or more. If it chances that the flagellum was the only one given off from the mother parasite, the pigment of the latter becomes motion-

less, the parasite quickly shrinks, and soon only a mass of pigment and degenerated material remains.

In the second case, after persisting for some time, from half an hour to an hour or more, the flagella gradually become motionless and disappear, while the pigment ceases moving and the body of the parasite shrinks, becomes vacuolated, and soon presents a mere clump of debris.

In the third case, after a certain time, the flagella become less actively motile and appear to become entangled with the body of the parasite, thus seeming to be folded about it, sometimes loops being formed by the attachment of a flagellum to the mother parasite. The pigment in the body of the parasite becomes motionless and the same degenerative changes occur as in the former case.

In the last case the parent parasite, either after the escape of one or more flagella or in cases where no escape takes place, breaks up into two or more parts, each part containing pigment, which remains in active motion for some time. On careful observation it will be seen that the fragments are united by very delicate hyalin threads. The flagella soon lose their motility and disappear, but the fragments containing the pigment may persist for a long while. In one case the pigment was seen to be in active motion in one of the fragments of such a parasite after a period of eight hours, at a room temperature of 70° F.

It is not often that one has the good fortune to witness the development of the crescent into a flagellated organism, and the following observation is therefore of importance. In observing a sample of blood from a case of estivo-autumnal fever, which was particularly rich in crescents, I observed a medium-sized crescent entirely enclosed within a red corpuscle, occupying about one-half of it. While under observation, the crescent suddenly seemed to expand into a round body, the pigment, motionless, occupying the center. After about ten minutes this round body suddenly became free, the red corpuscle seemed to melt away from around it, remaining as a pale shell close to the now free round body. Within a short time, probably about five minutes, the pigment within the round body became motile, at first slowly, then very rapidly, distributed throughout the protoplasm of the organism, and suddenly two flagella shot forth from opposite sides of the parasite. One of these afterwards became

detached and was lost sight of; the other, after persisting for about half an hour, ceased moving, and it and the body of the parasite became shrunken and degenerated. This observation conclusively proves two things: (1) that the crescents are developed within the red blood-corpuscles, and (2) that the active flagellated parasite is developed from the crescents. It will be noticed that in the above observation it was the active flagellated parasite which was developed, and not the passive form, which will now be described.

The Passive Flagellated Parasite (Estivo-Autumnal).—In the blood of those cases of estivo-autumnal fever containing crescents there will be noticed numerous round and oval bodies in which the pigment is arranged in a wreath-like form. These bodies seem to be of two kinds: First and most numerous are those in which the pigment is of rather dot-like or rod-like form, and fine, sometimes motile and sometimes not, and those, fewer in number, and almost always round, in which the pigment is arranged in large black or dark brown dots, in a perfect circle and almost never motile. From the first variety arises quite often the active flagellated organism.

The last-named round bodies merit a more minute description. They are clear-cut and definite, perfectly circular, and appear to possess a somewhat granular protoplasm; the pigment is arranged in round, very dark dots, forming a perfect circle, which may, however, be situated to one or the other side of the protoplasm of the organism. The pigment is generally non-motile, although occasionally a peculiar trembling motion may be observed; but the pigment retains its circular arrangement always, unless degenerative changes occur.

No matter how long such a round form is watched, it will never be seen to present the phenomena of exflagellation. The pigment does not become active and distributed throughout the protoplasm, nor do flagella emerge from within it; but in examining blood containing these bodies some of them are seen to possess one, two, or more flagella. These flagella are somewhat peculiar; they seldom possess a clubbed outer extremity, as is the case with the active flagellated body; but at their juncture with the round body a nodule is often noticed which resembles exactly the clubbed extremity of the flagellum of the active flagellated body. The movements, also, of these flagella are peculiar. Instead of the rapid serpentine lashings seen in the

PLATE I

THE QUOTIDIAN AND TERTIAN ESTIVO-AUTUMNAL PARASITES

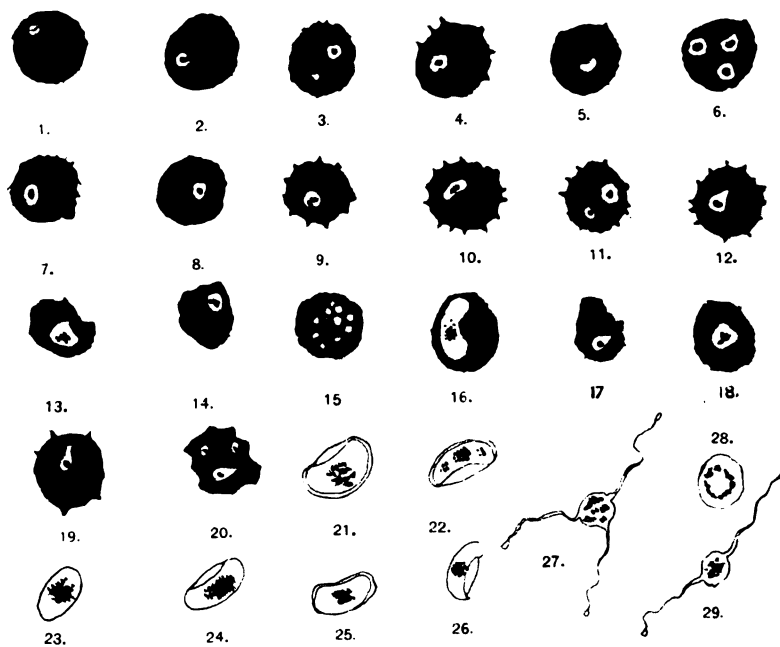
(The figures should be read from left to right)

The Quotidian Parasite. Figs. 1 to 29.

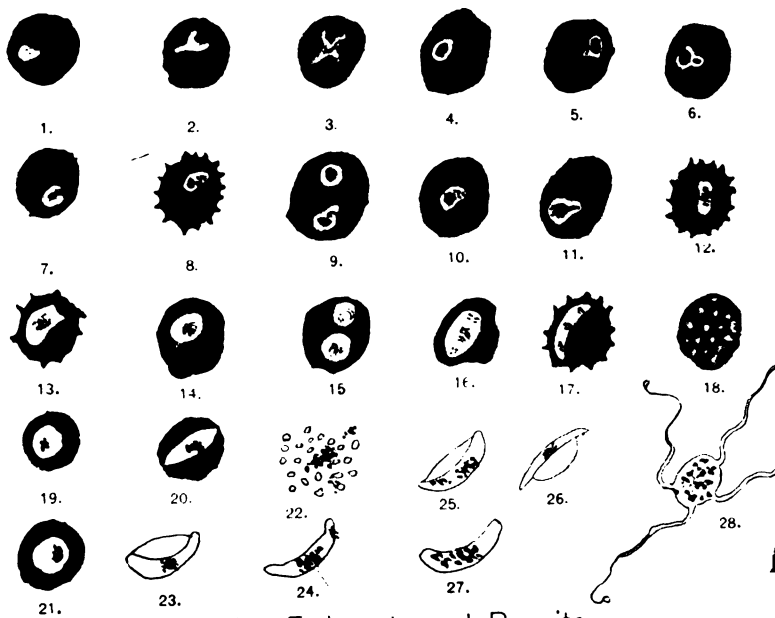
- Figs. 1 to 7. Ring-forms of the Quotidian Parasite.
- Figs. 8 to 10. Pigmented forms of the Quotidian Parasite.
- Fig. 11. One ring-form and one pigmented form.
- Figs. 12 to 14. Pigmented forms of the Quotidian Parasite.
- Fig. 15. Intracorpuseular segmenting form.
- Fig. 16. Intracorpuseular crescentic form.
- Figs. 17 to 20. Pigmented forms.
- Figs. 21 to 26. Crescentic forms of the Quotidian Parasite.
- Figs. 27 and 29. Flagellated forms of the Quotidian Parasite.
- Fig. 28. Preflagellate passive form of the Quotidian Parasite.

The Tertian Parasite.

- Figs. 1 to 5. Hyalin forms of the Tertian Parasites.
- Figs. 6 to 16. Pigmented forms of the Tertian Parasites.
- Fig. 17. Intracorpuseular crescentic Tertian Parasite.
- Fig. 18. Intracorpuseular segmenting Tertian Parasite.
- Figs. 19 and 21. Large pigmented forms of Tertian Estivo-autumnal Parasite.
- Fig. 20. Intracorpuseular ovoid form of Tertian Estivo-autumnal Parasite.
- Fig. 22. Extracorpuseular segmenting form of Tertian Estivo-autumnal Parasite.
- Figs. 23 to 27. Crescentic forms of Tertian Estivo-autumnal Parasite.
- Fig. 28. Flagellated form of Tertian Estivo-autumnal Parasite.



The Quotidian Estivoautumnal Parasite.



Tertian Estivoautumnal Parasite.



flagella, as put forth from the active parasite, the movements are of a different character. The flagella seem to straighten and then relax, revolving apparently very rapidly upon their axes; sometimes they may be seen to pull themselves loose from the round body and again become attached to it. In the meanwhile the pigment within the round parasite has maintained its circular arrangement, and is, at most, very slowly motile.

Sometimes no nodular swelling is noted at the point of attachment of the flagella, and in such parasites the pigment has a more rapid vibratory motion.

This same form occurs in tertian fever, but is larger, the pigment is less regularly arranged, and it is very much more rare.

The question arises: What do these forms of the malarial parasite signify? A few months ago, in a conversation with Dr. Thayer, he mentioned their occurrence, which I had noted but had not paid much attention to. Since that time I have convinced myself that these forms occur, not as a rarity but very often, and that they represent, as has been suggested by McCallum, the efforts of flagella, which have been set free in the circulation, to penetrate within the interior of a parasite, represented by the round bodies just described. While I have not been so fortunate as have McCallum, Thayer and others, as to have actually seen the disappearance of a flagellum within one of these parasites, I am convinced from what I consider sufficient evidence to prove the fact, that this does occur. From the appearance and character of the motion of the flagella, and the passive condition of the organism to which they are attached, it seems to be impossible to believe other than that these flagella are striving to push their way into the parasite, and the fact that flagella have been seen to become detached from the parasite and again attach themselves to it, is almost conclusive proof that such is the case.

The circle of events is then, I believe, as follows: The active flagellated organism is developed from the crescentic estivo-autumnal organism. Flagella are produced and liberated, the mother organism, her duty fulfilled, degenerating and perishing. The free flagella swim actively about among the blood-corpuscles until they come in contact with the peculiar, round, passive parasite, which they endeavor to penetrate. McCallum and Thayer have seen this penetration occur, one of the flagella becoming submerged, so to speak, within the substance of the parasite.

The nature of the process we are as yet ignorant of, but these two varieties of flagellated parasites do occur in the blood of malarial fever, and the observations upon them so far conclusively prove that the flagellate body is not a degenerative body, but is without doubt a very highly developed vital form of the plasmodium of malaria. It is but reasonable to suppose that these forms are calculated to preserve the life of the parasite outside of the human economy, as they arise only when the blood has been exposed to external conditions, and that we have in this process another proof of the extra-corporeal existence, in another form, of the malarial parasite.

The Origin, Nature and Significance of the Crescentic, Ovoid and Flagellate Bodies.—The crescents originate from young estivo-autumnal parasites, and their development has been carefully studied by Marchiafava and Bignami,* who say: "The young parasitic forms from which the crescents originate are distinguishable from other forms of this species of parasite even when they are less than a quarter of the size of a red blood-cell. They occur as small round, ovoid or spindle-shaped bodies, which, when seen in a fresh specimen, appear to be quite homogeneous and to contain a greater amount of black pigment than do the bodies of equal size of the preceding cycle; the pigment, however, is in the form of little rods, or somewhat larger granules, and is either irregularly disseminated in the body of the parasite or collected chiefly toward the periphery. These forms are not motile, they always occupy the lateral portion of the red corpuscle, and in their development always tend to adapt their convex surface to the edge of the corpuscle itself. As the development proceeds even the bodies, which were originally round, tend to take on a long ovoid or rather spindle-form, as long as the distance between the poles of the ovoid does not exceed the diameter of the red corpuscle; where it does, the body either keeps the same shape or it becomes curved and forms the true crescent."

It is very seldom that these young developing crescents are found in the peripheral blood, but blood from the spleen, and especially the bone-marrow, will show numbers of them; and it is generally believed that the bone-marrow is the point of origin of the crescents.

As has been already shown, the ovoid bodies develop from

*"Malaria, Twentieth Century Practice," Vol. XIX, page 44.

the crescents, and the preflagellate and flagellate bodies from the ovoids.

A volume could be written in considering the significance of the crescents, ovoids, and flagellate bodies, for the theories concerning them have been many and various. I shall consider here only the most important.

Canalis, Antolissei, Grassi, Golgi, Feletti, and others hold or held that the crescents were reproductive organisms, and multiplied within the human economy.

Grassi and Sakharov believe that they are a distinct species of parasite. Bignami, Marchiafava, and Celli believe the crescents to be sterile forms of the parasites, and this theory, modified so as to mean that the crescents are sterile forms only for the human life-cycle, is to-day regarded as the true one, and has the benefit of experimental evidence. Personally, I have never seen any evidence of segmentation or reproduction in crescents, and am convinced that they are forms which only undergo reproductive changes when removed from the human body, and after reaching the intestine of the mosquito.

As to the significance of the flagellate bodies, the theories have been even more diversified than in the case of the crescents. I have already referred to some of these theories. Laveran believed that the flagellated parasite was the completely developed malarial parasite, and that no parasite reaches perfection until it became flagellated. Grassi and Feletti held that they were degenerate bodies, while Dock regarded them as "resting forms," which, under certain conditions, were capable of again reproducing the typical parasite. This idea has been strikingly confirmed by the mosquito theory.

Mannaberg inclined to the belief that they were forms intended to perpetuate the life of the parasite outside the body, and Thayer inclined to the same belief.

Manson was one of the first to emphasize the hypothesis that the flagellate bodies were forms which began in man the life-cycle afterward completed in the mosquito, and by the labors of Ross, Marchiafava, Bignami, McCallum, and others, it has been proved beyond all doubt that the flagellated bodies are sexual forms which assist in the development of the parasitic form which completes its life-cycle within the mosquito.

Simond was the first to claim that the flagella were sexual forms, and he arrived at this conclusion from a study of the life-

cycle in other sporozoa, and further study by Schaudinn, Siedlecki, McCallum, and others have enlarged and verified the sexual theory. Thayer, Koch, Marchiafava, Bignami, and most other authorities have expressed their belief in this theory. Marchiafava and Bignami say, regarding this: "Reasoning from analogy, therefore, it seems probable that the forms which pass from man to the mosquito are sexual forms, and that an act of fecundation initiates the new life-cycle in the middle intestine of the insect."

I believe that the history of the development of the parasite is probably then as follows:

From the crescents are developed the ovoid bodies, and from these the round or preflagellate bodies. Certain of these round bodies become flagellated (the active flagellated body), while others do not. The first are male elements, the second female. The flagella (male elements) become free and penetrate and are received into the non-flagellated bodies (passive flagellated bodies, female elements), fertilizing them, and thus the new life-cycle is commenced. These phenomena occur in the middle intestine of some species of mosquito, and will be considered more fully in the succeeding chapter.

This theory has now the benefit of a large amount of experimental evidence, and it may be said that from the structure of the flagellum alone it would be almost impossible to believe other than that the flagella are intended to continue the propagation of the malarial parasite, as it has been demonstrated that nuclear chromatin is present within them. When to this fact is added the penetration of the round bodies by the flagella, as witnessed by McCallum and Thayer, the evidence is certainly convincing.

CHAPTER IV

THE LIFE-CYCLE OF THE ESTIVO-AUTUMNAL PARASITES WITHIN THE MOSQUITO

As far as is at present known, the malarial parasite only undergoes development within certain species of mosquito, i. e., the species belonging to the genus *Anopheles*. I am indebted to the works of Marchiafava and Bignami for a large part of the description of these mosquitoes, which follows: The mosquitoes belonging to the genus *Anopheles* are divided into two classes: those with and those without spotted wings. Of the first, there are the *Anopheles bifurcatus* and *Anopheles nigripes*. They are all small dark insects, either brownish black or brownish yellow in color.

Of the last variety, or *Anopheles* with spotted wings, there are the *Anopheles claviger* and *Anopheles pictus*. The *Anopheles claviger* has wings marked by four black spots, the remainder of the wings being brown or yellowish brown in color.

The *Anopheles nigripes* has a blackish brown wing and yellowish spots along the margins. These spots are three in number, the center being the largest, and the posterior the smallest, while on the remaining portions of the wing there are from five to seven brownish spots.

An easy way to distinguish the *Anopheles* was said to be by noticing the position which the insect assumes when resting upon an object. The body of the *Anopheles* is always vertical to the object lighted upon, while the body of the genus *Culex* is horizontal. This assertion has been proved false, and they are most easily distinguished in the larval stage.

METHODS OF STUDY.—Those who have studied the life-cycle of the malarial parasite within the mosquito have used mosquitoes within a glass tube, open at one end. This end is placed in contact with the skin of the person experimented upon, and the insects allowed to bite. The mosquitoes are then placed in a suitable receptacle and kept in a room having a temperature of from 70° to 80° F.

The following directions regarding the preparation of the mosquito for study are taken from Marchiafava and Bignami's masterly article upon "Malaria" in Volume XIX of the "Twentieth Century Practice of Medicine." They say: "As the life-phases of the parasite are observed in the mid-intestine and the salivary glands, the preparation of these parts is of great importance."

"To prepare the middle intestine, the mosquito is anæsthetized by ether or tobacco smoke, and then fixed upon a piece of colored glass by means of a needle passed through the thorax, with the back towards the glass; then with teasing needles we press lightly at about the third abdominal segment, and very gently push apart the two needles, making gentle traction. By this means we draw out the whole intestine; the anterior intestine is ruptured at the thoracic segment, the posterior intestine remains adherent to the last abdominal segments, which are detached from the others, and the middle intestine, the most important for our researches, remains free. All this takes place in a small drop of physiological salt solution or in a weak solution of 1 to 2 per cent formalin.

"To prepare the salivary glands we proceed as follows: Holding the thorax fixed, as described, we detach the head by slight traction with the needle, and thus sometimes succeed in extracting all the glandular tubes with their excretory ducts; if this does not occur we shall have to tear off the anterior half of the thoracic segment with two fine teasing needles.

"Fresh preparations, obtained in this manner, are examined in the sodium chloride or the formalin solution."

To obtain permanent stained specimens the mosquito is hardened in alcohol or bichloride, imbedded in paraffin and sectioned, the sections being stained with hemotoxylin or methylene blue.

HISTORICAL.—The history of the discovery of the rôle played by the mosquito in malaria is one full of interest, but is so extensive that it can only be touched upon here.

Nuttall* states that nearly two thousand years ago the Roman writers Varro, Vitruvius and Columella mentioned the idea that mosquitoes bore a causal relation to malaria. Nott, in 1848, referred to it, and King, in 1883, wrote an excellent plea in its favor. Laveran, Pfeiffer, and Manson have advocated it in

*"Centralblatt für Bacteriologie," etc., Feb. 14-21-23 and March 18. 1899.

their writings. Bignami, in 1894, did some experimental work along this line, which resulted negatively. To Manson, of England, belongs the credit of re-awakening an interest in the subject, and in his Goulstonian lectures, in 1898, he formulated a hypothesis, which very largely has been proven true by later experimental workers. To Ross, Bignami, Daniels, Dionisi, Bastianelli, Grassi, and Marchiafava the world is indebted for the knowledge of a new etiological factor in the production of malaria, i. e., the mosquito; and it is not too much to hope that in time this knowledge will lead to the suppression of one of the greatest foes of humanity and civilization.

The development of the crescentic malarial parasite has been studied in the tissues of the mosquito by Grassi, Bignami and Bastianelli and by Ross and Daniels. In the description which follows I have quoted largely from Bignami, whose studies in this subject have been most extensive and excellent.

The Development of the Crescentic Parasite within the Mosquito (Anopheles claviger).—I have already considered the fertilization of certain of the crescents by the flagella. This process, evidently sexual, takes place within the middle intestine of the mosquito. The crescents are known, biologically, as *gametes*, the male elements or active flagellated bodies as *micro-gametocytes*, the flagella as *micro-gametes*, while the bodies which do not become flagellated, i. e., the passive bodies or female elements, are known as *macro-gametes*.

If an *Anopheles claviger*, which has been allowed to suck the blood of a person suffering from estivo-autumnal fever, crescents being present, and kept in a vessel having a constant temperature of 86° Fahr., be examined, the following phenomena will be noted:

If the middle intestine be examined about forty hours after the insect has sucked the infected blood, the intestinal wall will be found to contain spindle-shaped bodies, identical in appearance with those observed in human blood, save that they are larger. Often similar bodies are observed, but more oval in contour. These bodies are pigmented, but the pigment instead of being in a clump or scattered, as is the case in the human body, is arranged around the periphery. The bodies alluded to are situated on the outer side of the epithelium and basement membrane of the intestine, between the adipose tissue and muscular wall of the intestine, that is, they are within the substance of

the intestine. After the second day the developmental changes are more rapid and noticeable.

Examined on the third or fourth day it will be seen that these bodies have increased much in size, and the protoplasm is granular and reticular in appearance. The pigment is less in amount, while the entire parasite is enclosed within a well-defined capsule.

On the fifth day the increase in size is astonishing, the parasites increasing to 70μ , or even more, so that they project from the intestinal walls, like bots in a horse. Within them are numerous minute bodies which are nuclei, and peculiar shining bodies which resemble fat. The capsule is very distinct.

On the seventh day the interior of the parasite contains an immense number of very delicate filaments, having thinned extremities, each containing at its center a small amount of nuclear chromatin. These filaments are about 14 mm. in length and arranged like rays about a central mass, which may contain some black pigment. The capsule is very distinct. These filaments are the sporozoites. If the intestine be examined at a later day than the seventh, it will be found that the capsule has ruptured, thus setting free the sporozoites, and the remains of the capsule will be seen surrounded by the liberated sporozoites.

If now the tubules of the salivary glands be examined, they will be found often crowded with these liberated sporozoites, and it is at this time that in biting a man the mosquito inoculates the *sporozoites*, which, after undergoing certain changes as yet undetermined, and which take place during the period of incubation, become the hyalin, intracellular, estivo-autumnal parasite.

Peculiar brown bodies are also found in the encapsulated parasite within the mosquito, which vary in size and shape, being rod-like and round, straight or curved, and are considered to be degenerative bodies.

Summing up, then, our knowledge of the life-cycle of the estivo-autumnal malarial parasite, it would be as follows:

Human Cycle—

1. Sporozoite.
2. Hyalin amœboid body.
3. Pigmented body.
4. Segmenting body.
5. Crescentic body.

Mosquito Cycle—

1. Crescentic body (gametes).
2. Round, passive, flagellate body (macro-gametes) .
3. Round, active, flagellate body (micro-gametocytes).
4. Encapsulated, cystic body.
5. Sporozoites.

The conclusive experimental evidence in regard to the inoculation of estivo-autumnal malarial fever by the mosquito will be considered in the chapter upon etiology.

In distinguishing between mosquitoes of the genus *Anopheles* and those of the genus *Culex*, the following points are to be observed, during the stages of development of the insect:

The Eggs.—The eggs of *Culex* are deposited in boat-shaped masses, containing from 200 to 400 eggs. Those of *Anopheles* are arranged loosely upon the surface of the water.

Larval Stage.—The larva of *Culex* comes often to the surface of the water to breathe, and its position is at an angle of 45 degrees to the surface, while the larva of *Anopheles* remains always at the surface of the water and lies parallel to it. They also differ markedly in their structure.

Pupal Stage.—The *Culex* is much more perpendicular to the surface of the water than the *Anopheles*.

Adult Stage.—The palpi in the female *Anopheles* are much longer than those of *Culex*.

The position of *Culex* when quiet is angular, while that of *Anopheles* is horizontal.

Howard and Thayer have determined that the *A. quadrimaculatus* found in this country is identical with the *A. maculipennis* of Italy.

CHAPTER V

CULTIVATION AND INOCULATION EXPERIMENTS—PHAGOCYTOSIS CLASSIFICATION

CULTIVATION.—It may be said with certainty that no one has been able, as yet, to cultivate the malarial parasite in artificial media outside the human body.

Coronado,* a Spaniard, is the only investigator who has even claimed to have done so, and his experiments have been repeated by other observers, none of whom have been able to confirm his results. He claimed to have successfully cultivated the parasites in water, which was infected. Such water, together with mud from the bottom of the infected pool, when placed in test-tubes, gave, according to him, cultures of the parasites, and the entire cycle could be followed. As stated, no other observer has been able to confirm his results, and in the light of our present knowledge they are evidently erroneous.

The estivo-autumnal parasites have been kept alive outside the human body for some days. Sakharov† was the first to perform such experiments successfully, and he found that the parasites were alive in blood obtained by leeches from the human subject after a week, provided the leeches were kept upon ice. The parasites underwent no reproductive changes, however. Blumer was able to confirm these experiments.

Hamburger and Mitchell have performed similar experiments, which, as quoted by Thayer,‡ were as follows:

"Mr. Hamburger took the blood from a case of estivo-autumnal fever with quotidian paroxysms at a time when only small amœboid and ring-shaped, non-pigmented hyalin bodies were present. During the next several days he was able to distinguish a slight increase in size, with the accumulation, in nearly every organism, of a few small, motile pigment-granules. On the eighth day the organisms were distinctly visible, each

*"Cronica Medici Suiurgica de la Habana," Nov., 1892.

†"Jahresbericht," Reference in Baumgarten's, 1890, p. 444.

‡"Lectures on the Malarial Fevers," 1897, p. 27.

with a small group of slightly motile granules in the middle or at some point on the periphery of the parasite.

"Mr. Mitchell placed a leech upon an individual suffering with a combined estivo-autumnal and double tertian infection. The blood showed two groups of active tertian organisms and a few crescentic and ovoid forms. In the body of the leech the tertian organisms were to be made out for ten days. The pigment was active for four days, but no amoeboid movement was to be made out in the parasites. The crescentic and amoeboid bodies remained unchanged; no flagellate forms were observed."

In the light of the recent experiments with mosquitoes, it is interesting to note that in the leech the crescents and ovoids underwent no further development, and the flagellated parasites were entirely absent.

INOCULATION EXPERIMENTS.—Many observers have been successful in producing malarial fever by inoculating a healthy individual with blood from one suffering from the disease. It would be unprofitable here to detail all the experiments which have been performed along this line. Suffice it to say that among those who have successfully produced the disease in this way, may be mentioned Gerhardt, Mariotti, Ciarrochi, Marchiafava, Celli, Gualdi, Antolisei, Angelini, Di-Mattei, Baccelli, Sakharov, Bignami, and Bastianelli.

It has invariably been found, when such experiments have been carefully conducted, that the type of parasite inhabiting the blood injected is found again in the blood of the individual infected, and is followed by the clinical symptoms of that variety of malaria produced by the type of parasite injected.

In other words, the subcutaneous inoculation of blood from a person suffering from tertian estivo-autumnal fever into a healthy individual is followed by the occurrence of tertian estivo-autumnal fever in that individual, and this fact proves conclusively that there are varieties of the malarial parasite, each capable, and capable only, of producing the characteristic clinical symptoms with which it is always associated.

As these experiments are of great value and interest, I give in detail two in which the estivo-autumnal parasites were inoculated.

The first, performed by Di-Mattei,* is of interest because two types of fever were produced at different times. The patient experimented upon had suffered from quartan malaria some time

*Preliminary Note, "Riforma Medica," 1891. No. 121, p. 544.

previously, and had recovered. He was inoculated with blood from a case of irregular fever, which showed only crescents at the time of inoculation. About eight days after inoculation the patient's blood showed non-pigmented, hyalin parasites. No fever occurred until sixteen days after inoculation, and it was nine days after the onset of fever before crescents were found in the blood, or twenty-five days after inoculation. Di-Mattei followed this experiment by injecting into the same patient blood from a case of quartan malaria, and in fifteen days quartan fever appeared and quartan parasites were present in large numbers in the blood. The second experiment which I shall quote was performed by Sakharov* upon himself. He allowed leeches to suck the blood of a case of pernicious malaria, which was comatose, and whose blood contained immense numbers of hyalin, non-pigmented ring-forms of the estivo-autumnal parasite. The leeches were kept upon ice for four days, at the end of which time he injected 1 cubic centimeter of blood from one of them into his arm.

At the end of twelve days he had a malarial paroxysm, accompanied by a chill, which was repeated upon the following day. An examination of his blood showed numerous typical non-pigmented "ring-forms" of the estivo-autumnal parasites.

From the foregoing it will be seen that estivo-autumnal fever can be transmitted from man to man by inoculation.

PHAGOCYTOSIS.—In examining the blood of patients suffering from estivo-autumnal malarial fever, in almost every case it will be noticed that many of the white cells or leucocytes contain malarial pigment, portions of malarial parasites or even the whole parasite. These leucocytes are the so-called phagocytes which are always present in malarial blood at some time.

These pigment-containing cells were noticed in the blood before the parasite of malaria was discovered, and Laveran, Marchi-fava, Celli, Golgi, Metchnikoff, Bignami, Osler, Barker, Dock, and Thayer have all added to our knowledge concerning these cells. In the tertian and quartan fevers they were noticed to be most numerous during or just after the paroxysms, while in estivo-autumnal fever they occurred at less regular intervals.

Two theories have been advanced regarding the phagocytes, one, advocated by Metchnikoff† and his followers, that phagocytosis in malaria is an active protective process, and is the cause of

*"Cent. für Bakt.," Feb. 5, 1894, XV. Nos. 5 and 6.

†Russk. Med., 1887. No. 12, p. 207.

spontaneous recovery; the other, advocated by Bastianelli, that it has but little to do with spontaneous recovery and that the facts are not sufficient to prove that the phagocyte is, as Metchnikoff believed, an active enemy of the malarial parasite.

From my own observations I must admit that I have seen but little to prove Metchnikoff's theory, and while I admit that an active phagocytosis is undoubtedly of benefit to the patient, in that a certain number of parasites are destroyed and much pigment and debris removed from the blood by them, I believe that it has little to do with spontaneous recovery from the disease.

The Phagocytic Cells.—The phagocytes are the polymorphonuclear, and the large mononuclear leucocytes, especially the latter. The eosinophiles and lymphocytes are not phagocytic in their action, and when pigment is seen within them it is, without doubt, accidental.

Although the leucocytes, as a whole, are decreased in number in malaria, it is true that the phagocytic varieties are relatively, as a rule, increased; and this fact is one of the strongest arguments in favor of Metchnikoff's theory as applied to malaria.

Besides the varieties of leucocytes mentioned, certain other cells are phagocytic in malaria. Among these are endothelial cells (rarely), the cells of the splenic pulp—especially macrophages—and cells of the marrow of the bones. In cases of pernicious estivo-autumnal malaria, examination of all these cells show them crowded with pigment and parasites. This is especially true of the macrophages of the spleen. These immense cells, from ten to twenty times as large as small leucocytes, will be seen to contain great blocks of pigment, parasites in various stages of development, and even entire infected red corpuscles.

The phagocytes undergo certain degenerative changes, and such cells are most numerous in the blood of pernicious cases. The degenerative changes are: vacuolization, fatty degeneration, and fragmentation of the nucleus. These changes are most common and marked in the large mononuclear cells or macrophages.

Time of Occurrence of Phagocytosis.—In the intermittent fevers, quartan and tertian, phagocytosis is most marked during or directly after the paroxysm, and this is true, also, in cases of uncomplicated tertian and quotidian estivo-autumnal fever, during an acute attack. If, however, the disease has persisted for a long while, or there is a double infection, the cyclic appearance of the phagocytosis cannot be demonstrated without repeated observa-

tions and most careful study, and often not even then. In pernicious cases phagocytes are, as a rule, very numerous, especially the large mononuclear variety or macrophages. Quinine tends to increase phagocytosis, especially in pernicious cases. In many cases of severe estivo-autumnal infection an examination of the blood always shows a marked phagocytosis, and in such cases it is impossible to ascertain the cyclic occurrence of the process. This is no doubt due to the rapid multiplication of the parasites.

Substances taken up by the Phagocytes.—In the estivo-autumnal malarial fevers the following are found within the phagocytes: first and most common, free pigment; second, flagellate organisms; third, shrunken and degenerated red cells, both with and without parasites (these occur wholly within macrophages); fourth, segmenting forms (common in blood from the spleen, etc.); fifth, crescentic and ovoid forms (very rarely). The amount of pigment which the phagocytes absorb is very great, and there can be no doubt that they are of vast use to the organism in taking from the small capillaries this pigment, which might so easily occlude them.

There is no more remarkable or beautiful object lesson in all pathology than the engulfing of a flagellated malarial parasite by a phagocyte, as it is often observed under the microscope, and in no other disease is phagocytosis so well illustrated.

Significance of Phagocytosis.—I have already considered the question of the relation of phagocytosis to spontaneous recovery, and have noted the fact that it is just as active in fatal cases as in those which recover, as a rule, even more active. The question now arises: Has phagocytosis, in the estivo-autumnal fevers, any prognostic import? I answer unhesitatingly, yes. The greater the phagocytosis is in any given case of tertian or quotidian estivo-autumnal malarial fever, the more severe is the infection and the more grave the prognosis. Especially is this true if, in the circulating blood, are found numerous large mononuclear phagocytes or macrophages. From my own observations I am convinced that a marked phagocytosis in estivo-autumnal fever, far from being a favorable sign, is almost typical of a pernicious infection, and if no cyclical course can be traced after many examinations, is absolutely typical and should be the signal for the institution of the most energetic measures for the treatment of the disease. If neglected or treated improperly, such cases almost invariably terminate fatally.

CLASSIFICATION.—The great majority of zoölogists place malarial parasites among the Sporozoa, and some place them among the Rhizopoda.

Laveran proposed the name *Oscillaria malarix* for the parasites. Marchiafava and Celli gave us the term *Plasmodium malarix*, which is to-day the name generally used in describing the parasites. I have already mentioned the objections to this name and will not further discuss it here.

There are three classifications which are of interest, those of Labbe, Kruse, and Grassi and Feletti.

Labbe's Classifications.—Labbe classes all the blood-parasites in the Sporozoa and divides them into two classes: Hæmosporidia and Gymnosporidia, in the latter division placing the parasites of man, which he well names Hæmamœba Laverani. In this same division he places the Halteridium and Proteosoma of birds.

Kruse's Classification.—Kruse considers the Sporozoa as divided into six orders, the blood parasites belonging to the order Hæmosporidia. He subdivides the Hæmosporidia into four genera, as follows: 1, Hæmogregarina (lizard, turtle); 2, Drepanidium (frog); 3, Hæmoproteus (birds), and 4, Plasmodium (man).

Grassi and Feletti's Classification considers that the malarial parasites belong to the Sarcodina, and divides them into two genera, as follows: 1, Hæmamœba: *H. malarix* (quartan parasites); *H. vivax* (tertian); *H. præcox*, and *H. immaculata* (estivo-autumnal parasites); also parasites of birds; *H. relicta*; *H. sub-præcox*; *H. subimmaculata*. 2, Laverania; *L. malarix* (crescent forms); *L. ranarum* (frog), and *L. Danilewsky* (birds).

These classifications are chiefly of zoölogical interest, and, as yet, no one of them has been decided upon as undoubtedly correct.

VARIETIES OF ESTIVO-AUTUMNAL PARASITES.—In considering the subject of classification of the malarial parasites, the question arises, Are there different species or varieties of the estivo-autumnal parasites, and can these different species be recognized both morphologically and clinically? In answer, I have already expressed my opinion that there are at least two distinct varieties of the estivo-autumnal parasites, which, after sufficient practice, can be easily recognized by the microscope, and which, if alone and uncomplicated, give rise to perfectly distinct and characteristic clinical signs.

Marchiafava and Bignami, in differentiating the tertian and quotidian estivo-autumnal parasites, call attention to the following: 1. Duration of life-cycle—twenty-four hours in the quotidian, forty-eight hours in the tertian parasite. 2. Pigmentation, greater in the tertian, the pigment motile. 3. Size of parasite, greater in the tertian. 4. Amœboid motion, more marked in tertian and longer preserved. 5. Relation of the various forms to the life-cycle.

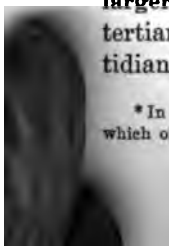
In my researches I have confirmed most of Marchiafava and Bignami's conclusions, and in the numerous cases of both varieties of estivo-autumnal fever studied, have, I believe, been able to trace marked differences in every developmental stage of the parasites. I have already referred to these differences but will recapitulate them here:

1. *The Hyalin Stage.*—The tertian estivo-autumnal parasite is larger, more clearly cut and refractive, and has more sluggish amœboid motion than the quotidian parasite; it has often a signet-ring shape, while the quotidian is perfectly round. Only one parasite is found, as a rule, in a corpuscle in tertian infection, while in quotidian two or more are common. The infected corpuscle is less crenated and lighter in color when infected by the tertian parasite.*

2. *The Pigmented Stage.*—The tertian parasite is larger, and pigmentation occurs while the "ring-form" is still retained; in the quotidian the ring-form is never pigmented; amœboid motion is present after pigmentation, while in the quotidian it is always lost before pigmentation occurs; the tertian parasite is more sharply defined, and the pigment, present in larger amount, is finer, and is motile, while in the quotidian the pigment is always motionless and consists of one or two coarse granules. Only one pigmented tertian parasite occurs in a corpuscle, while two or more quotidian parasites may be present in one corpuscle; the infected corpuscle is more crenated and brassy when infected by the quotidian parasite.

3. *The Segmenting Stage.*—The number of segments is greater in the tertian, and the segments are more oval in outline and larger. Segmentation occurs outside the red corpuscle in the tertian estivo-autumnal parasite more often, while in the quotidian it occurs within the infected corpuscle.

* In the very young forms the tertian parasite is not as sharply defined as is the quotidian, which often looks as though it had been cut into the infected corpuscle.



4. *The Crescent Stage*.—The tertian crescents are longer and more narrow than the quotidian, are more deeply pigmented and have less often a double outline. The protoplasm of the tertian crescent is more refractive and granular in appearance.

5. *The Flagellate Stage*.—In the tertian parasite both forms of flagellate bodies heretofore described are larger and more deeply pigmented than in the quotidian.

6. *The Cycle of Development*.—Twenty-four hours complete the cycle of development within the human body, in the quotidian parasite; forty-eight hours in the tertian.

When we add to these numerous morphological differences the typical clinical phenomena exhibited by these parasites, it must, I think, be admitted that there are at least two varieties of the estivo-autumnal malarial parasite, a tertian and a quotidian; and from my own observations I can arrive at no other conclusion. The clinical differences will be dealt with fully in the section devoted to the description of the symptoms of the various forms of the fever.

It may be urged that the differences noted may be due to the special conditions of environment, or unusual factors affecting the health of the individual, etc., and while, of course, we are unable to prove that this may not be so, yet they are so constant and harmonious that it is impossible to believe that they are accidental, and until such theories can be proved I shall continue to believe that the estivo-autumnal malarial parasites are divided into at least two varieties, the quotidian and tertian parasites.

CHAPTER VI

EXAMINATION OF THE BLOOD — METHODS OF STAINING — THE STRUCTURE OF THE ESTIVO-AUTUMNAL PARASITES AS RE- VEALED BY STAINING

METHODS OF EXAMINING THE FRESH BLOOD.—There is no one thing more essential to success in recognizing the estivo-autumnal parasites in the blood than practical experience in the appearance of normal blood and the blood of other pathological conditions. He who supposes that he has only to look into his microscope at a specimen of blood, from a case of remittent malarial fever, to find the parasite, without having had previous experience in blood-work, will invariably be disappointed, and will give up the search in disgust. Success might possibly attend the search of such a tyro in the case of the large, fully grown, ordinary tertian malarial parasite, but never when the minute hyalin ring forms of the estivo-autumnal are concerned. The first thing, then, is some practical experience in examining the blood in health and disease and an intelligent conception of what one expects to find.

The first essential to success is a good microscope, having an Abbé condenser, a mechanical stage, and a first-class one-twelfth-inch oil-immersion lens. The latter is absolutely essential in examining the blood for estivo-autumnal parasites, and nothing less than such a lens should be thought of.

The same may be said, perhaps in a lesser degree, of the mechanical stage. It increases the chance of finding the organisms very greatly, and this fact, together with the infinitely greater ease of manipulation, is worth far more than the slight additional cost of such a stage.

To knowledge, experience and a good microscope should be added energy and a large store of patience, for often a half-hour's search will be rewarded by finding but one parasite, and sometimes will go unrewarded.

The following procedure is recommended in obtaining fresh blood for examination. The lobe of the ear or the top of the

finger may be used, the ear preferably. The ear-lobe or finger is washed with alcohol and wiped dry. A perfectly clean cover-glass and slide are at hand, and the slide slightly warmed by rubbing it gently. This facilitates the spreading of the blood. The ear-lobe or finger is pierced with a lancet or surgical needle, and the first and second drops of blood wiped away; the cover-glass is then touched gently to the summit of the next blood-drop and placed carefully upon the slide. If the cover-glass is thin, and the drop of blood on the glass small, the blood will spread evenly and quickly. If it does not, very slight pressure upon the cover-glass will suffice to spread the blood and will do no harm. Upon examining the specimen, if it is found that the blood-cells are in clumps or rouleaux, it should be discarded and one obtained in which the corpuscles are spread singly over the field. The preparation of the specimen should take as little time as possible, as exposure of the blood to the air crenates the red cells and injures the chance of finding the parasites. A little practice will enable one to secure suitable specimens for examinations very quickly. Fresh specimens of blood will keep for a considerable length of time at room temperature—for several hours—and I have repeatedly found such specimens well enough preserved after twelve hours to distinguish the malarial parasites. If the cover-glass is sealed with vaseline the specimen will keep much longer.

OBJECTS APT TO BE MISTAKEN FOR ESTIVO-AUTUMNAL PARASITES.—There are certain degenerative changes present in the red corpuscle at times, both in health and disease, which resemble the estivo-autumnal malarial parasites very closely—so closely, sometimes, as to deceive practiced investigators. The chief are: crenations, retraction of hemoglobin, vacuoles, and certain areas devoid of hemoglobin.

Crenations occur if the blood is exposed long to the atmosphere, or if the slide or cover-glass is not clean, and are confusing to an inexperienced observer if looked down upon directly, as they appear like round, rather hyalin bodies within the red corpuscle.

Retraction of hemoglobin is often observed at some point on the periphery of the red corpuscle, and consists of small semi-circular areas devoid of hemoglobin.

Vacuoles.—There is no more deceiving object in the blood than a small vacuole within a red corpuscle. Sometimes, especially if the border of the vacuole alters in shape, the resem-

blance to the hyalin disk-form of the estivo-autumnal tertian parasite is very marked. I have time and again had such vacuoles shown to me for plasmodia by experienced microscopists who had had but little practice with malarial blood. The greater refraction of the vacuole easily distinguishes it from a parasite.

Areas without hemoglobin occur in the red cells in certain diseases, as typhoid, tuberculosis, pneumonia, etc., and vary in shape. They may be situated at any part of the corpuscle, and may be round, spindle-shaped, oval, or ring-shaped. Some of them, especially the oval- and spindle-shaped ones, contain a minute dot, near the center, which resembles pigment. While these bodies are deceiving to the inexperienced, the absence of amoeboid movements and the much greater degree of refraction should serve to differentiate them from the malarial parasites.

STAINING METHODS.*—Where it is impossible, for any reason, to examine suspected blood in the fresh condition, reliance must be placed upon stained specimens for diagnostic purposes; but only then. When, however, we wish to study the structure of the parasite of malaria, stained preparations are most valuable, and it is from them that we have learned much of the finer morphological characteristics of the various organisms.

There are many ways of staining the parasites of estivo-autumnal malarial fever; but a description of a few of the most useful is all that will be attempted here. The blood-smears are prepared by carefully cleaning the lobe of the ear, puncturing it with a sterile needle or lancet, touching a clean cover-glass to the resulting drop of blood, and placing another cover-glass over it. The two are then slid very gently and carefully apart, and the smear allowed to dry. Care should be used not to get too much blood upon the first cover-glass, and to use no pressure in sliding the glasses apart. After drying, the smears are allowed to harden in equal parts of alcohol and ether for half an hour, when they are ready to stain. The plasmodia are stained by nearly all basic anilin dyes, but not by the acid dyes.

For staining I use either Romanowsky's or Chenzinsky's method, the latter preferably. Romanowsky's method is as follows: Two solutions are used—solution No. 1, a saturated aqueous solution of methylene blue; solution No. 2, a 1 per cent watery solution of eosin. The methylene blue solution

*A portion of this section is taken from an article by the author in the "Medical News" of November 3, 1900.

should be at least one week old. The staining solution is made fresh each time it is used, and consists of one part of the filtered methylene blue solution added to two parts of the eosin solution, and thoroughly mixed. The smears are placed face down upon this solution and are allowed to stain from one-half to three hours or more. The best results are obtained after about two and a half hours' staining. By this method, the red corpuscles are stained red by the eosin and the parasites a deep blue by the methylene blue. Romanowsky believed that the nuclear chromatin stained a violet color, but I had never, until recently, been able to confirm his observations. Although very beautiful stained specimens can be secured by this method, I much prefer the method of Chenzinsky, for the reason that it gives a more natural appearance. By Romanowsky's method, and, in fact, by most methods, the coloring by eosin is very vivid, especially that of the red corpuscles; whereas, in Chenzinsky's method the red corpuscles are stained more dimly, appearing almost natural in color, while the parasites are stained a fine blue, fully as well as by any other method.

Chenzinsky's method is as follows: A concentrated alcoholic methylene blue solution, diluted one-half with water, is added to an equal amount of a one-half per cent solution of eosin in 60 per cent alcohol. This solution is bottled and kept, and improves in staining qualities by age. The specimens are stained with this solution for five minutes, and then washed in water, dried, and mounted in Canada balsam. Much better specimens are obtained by staining for two hours or more, and I have secured very fine specimens by leaving the smears in the staining solution over night.

There are numerous other methods of staining the malarial parasites, but these are the most satisfactory and useful.

A word as to the use of stained preparations for diagnostic purposes: I am aware that a few authorities are staining preparations almost entirely for diagnosis, but I believe that it is a cumbersome and very unreliable practice. Where it is impossible to keep a specimen of blood fresh enough to look at under the microscope, the use of stained preparations is, of course, necessary; but where it is possible to examine the blood fresh, it is always to be preferred, as it is infinitely more exact and satisfactory. I have seen many cases where the fresh blood showed numerous ring-forms of the estivo-autumnal parasites, in which

smears taken at the same time and stained most carefully showed either none, or at most a very few dimly-colored parasites. There is also the danger of mistaking stained granular matter or débris lying upon the corpuscles for the small estivo-autumnal parasites in the smears, and this mistake can be very easily made by one who is unaccustomed to examining such preparations. The only strictly scientific way of diagnosing the various forms of the malarial parasites is by the microscopical examination of the fresh blood, and after all most specimens of blood will keep in a suitable condition for examination, under ordinary circumstances, for six, eight, or even a greater number of hours.

Before considering the staining reactions of the plasmodia, a brief note as to the recent staining method devised by Fitcher. It is to be recommended wherever speed in staining is desirable, where the fresh blood cannot be examined and a speedy diagnosis is essential. It is as follows: The smears are hardened in a 1 per cent solution of formalin in 90 per cent alcohol for from a half to one minute. They are then dried and stained for from twenty to thirty seconds in the following solution of thionin, known as Marchand's:

Saturated solution of thionin, in 50 per cent alcohol . .	20
Two per cent solution of carbolic acid	100

The solution should stand several days before using. After staining, the specimen is washed in water, dried, and mounted in Canada balsam. The red corpuscles are stained a very slight greenish hue, while the parasites are deep violet in color. Care should be taken not to stain for too long a time, and not to allow the formalin solution to act long, as it seems to cause a degeneration and vacuolization of the red cells. The method stains the estivo-autumnal rings very satisfactorily.

Laveran* has very recently devised a staining method which is a most excellent one, although I prefer either Romanowsky's or Chenzinsky's method. It is as follows: Three staining solutions are employed.

Solution No. 1: Silver oxide methylene blue (Borrel blue) is mixed with 150 cubic centimeters of distilled water in a flask. Enough of the crystals are used to form a nearly saturated solution. When the crystals are dissolved, the flask is filled with a solution of soda, and shaken, which causes a black precipitate of

*"Comptes Rendus, Soc. de Biologie," June 9, 1900.

silver oxide to be deposited. This is washed carefully, and an aqueous saturated solution of medicinal methylene blue is poured over it, and allowed to stand for eight days, shaking occasionally.

Solution No. 2: An aqueous solution of eosin, 1 part to 1,000.

Solution No. 3: A 5 per cent aqueous solution of tannin.

The stain is prepared just before using as follows:

Solution No. 1	1 c.c.
Solution No. 2	4 c.c.
Distilled water	6 c.c.

Each should be filtered before mixing.

The blood-smears are fixed with alcohol for twenty minutes. Five to ten minutes' staining will suffice to stain the parasites. When stained, the specimen is rinsed and treated with the tannin (Solution No. 3) for a minute, then washed and dried. The stain is very delicate and reliable, staining the nuclei of the cells a deep violet, the red corpuscles a pink, the protoplasm of the parasites a pale blue, and the chromatin a violet-red.

I have had but little experience with this stain, but it is no doubt an excellent one, provided it is prepared and executed as described by Laveran.

THE STRUCTURE OF THE ESTIVO-AUTUMNAL PARASITES AS REVEALED BY STAINING.—The following observations upon the staining reactions of the estivo-autumnal parasites are the result of experience gained from the examination of large numbers of stained specimens, and data from the writings of other observers.

1. *Staining Reactions of the Ring-Forms of the Estivo-autumnal Parasites.*—The staining reactions are alike both for the quotidian and tertian estivo-autumnal parasites.

The stained rings present the following appearance: A more or less deeply stained, thin ring, encircling a round portion the color of the corpuscle. At some portion of the stained ring there may often be seen a granule or dot of chromatin stained a dark purplish red which may be situated at the edge of the ring, projecting into the central unstained portion. In fact, at this stage, the parasite consists of an outer deeply stained portion, the protoplasm of the organism; a very rudimental nucleus, represented by the deeply stained chromatin granule or granules, situated somewhere upon the inner periphery of the stained portion, and an inner round or oval unstained area, representing a nutritive vacuole; sometimes the chromatin is situated within this

unstained portion and separated from the stained portion of the parasite.

In the pigmented rings there is a deeply stained outer portion (the ring), in which are situated the pigment-granules, generally at the periphery; the deeply stained violet chromatin is larger and generally situated within the colored ring, and may be surrounded by a pale area.

2. *Staining Reactions of the Pigmented Disk-Form.*—As the parasites become larger, the ring-form is lost, and the following appearances are present in stained specimens: The entire parasite is colored blue, most intense in the outer portion and gradually fading as the center is approached. At or near the center may sometimes be seen a deep reddish violet or almost black dot or spot, evidently chromatin, surrounded by a pale, almost unstained area. The nearer the parasite is to segmentation, the less does the chromatin show, until just before segmentation, when it again becomes visible in rare instances.

Marchiafava and Bignami* claim that with Romanowsky's stain the chromatin-granules can always be differentiated, and they thus describe the staining reactions of the more fully developed parasites: "By this method, indeed, we find that some of the bodies with blocks of pigment [usually the smallest] are composed of a peripheral portion stained blue [protoplasm], and of a central or sub-central formed of granules or filaments stained red [chromatin], surrounded by a pale substance which remains almost or altogether unstained [nuclear juice]. By the sides of these are seen other bodies with pigment [usually larger than the preceding], in which are two or three clumps of chromatin, each one surrounded by a zone of pale substance. Thus by a successive series of division of the nuclear protoplasm we have the formation of a varying number of little round or oval bodies of chromatin which are readily stained and are compact in appearance, that is to say, without recognizable structure and apparently homogeneous. At this point occurs the division of the body with the block of pigment into daughter bodies."

3. *Staining Reactions of the Segments.*—Each segment or spore, when stained, is seen to consist of a round or oval pale blue mass of protoplasm, containing a minute, deep reddish violet granule of chromatin.

As the parasite develops, the chromatin increases gradually

*"Malaria," 1900, p. 39.

in amount, and tends to become arranged in granules or strings which are often very thickly packed together.

4. *Staining Reactions of the Crescents and Ovoids.* — The crescents and ovoids are seen, when stained by Romanowsky's method, to consist essentially of a central dimly stained vesicle, containing deeply stained reddish chromatin granules, surrounded or even invaded by rodlets and grains of pigment, which are in turn surrounded by the protoplasm of the crescent, which stains a beautiful blue. Surrounding the crescent is often seen a reddish-stained border, constituting the membrane of some authorities, but which is in reality the remains of the red blood-corpuscles which has become folded about the organism. This is the explanation, also, of the double outline so often seen around crescents, such an appearance being due to the retraction of the hemoglobin about the body of the parasite, which stains with eosin. The discovery that chromatin exists in the crescents does away entirely with the arguments of those observers who have regarded them as sterile bodies, incapable of further development under any condition.

The crescent-forms of the estivo-autumnal parasites present many interesting staining phenomena. In those crescents in which the pigment is collected near the center, the organism, as a whole, takes a rather dim blue color, the poles staining much more deeply, while the center, in which the pigment lies, is often unstained or but dimly stained (vesicular nucleus). At each pole, as a rule, may be seen a very deeply stained semi-lunar area extending to its periphery and covering the horns of the crescent. The appearance presented is that which would result had each horn of the crescent been dipped into a darker staining fluid and withdrawn. Between the deeply stained horns of the crescent, and lying within the more dimly stained protoplasm, are often seen very deeply stained round or oval spots irregularly distributed. In some crescents these deeply stained spots are very distinct, and occupy a large part of the protoplasm of the crescent. As a rule, the area in which the pigment lies, and immediately surrounding it, stains very faintly, or not at all, but it is not rare to see a darkly staining belt or band passing through the center of the crescent, seeming to divide it into two parts. This appearance, however, is not common and does not by any means prove the dual nature of the crescent. Surrounding the crescent, in the majority of instances, is a narrow eosin-

stained border, believed to be the remains of the red corpuscle in which the crescent was developed. This red-stained border does not always, however, entirely surround the crescent; sometimes it is observed only between the two horns, forming the so-called "bib;" sometimes it is absent there and present over the convex portion of the crescent; sometimes it can only be seen covering the horns or one horn of the crescent. It is often observed to be broken or ragged in outline and interrupted in places, thus suggesting the gradual disintegration of the red cell. Crescents are often observed which do not show any eosin-stained border, and in such cases we may assume that the destruction of the red cell is complete, and the crescent is free in the blood-plasma.

While the above description applies to the majority of stained crescents, many exceptions occur. Quite often crescents are observed almost uniformly stained throughout; others do not present the deeply stained spots or polar staining; others stain very dimly at one end and deeply at the other. In fact, it would be almost impossible to describe all the variations which may occur, but in the vast majority of examinations of stained crescents the description given will be found correct.

The ovoid bodies stain exactly as do the crescents, so far as I have been able to observe, save that the polar staining is not so pronounced.

5. *The Staining Reactions of the Flagellate Bodies.*—It is exceedingly difficult to stain the flagellate bodies, but Marchiafava, Bastianelli, Bignami, Manson, Gotye and others have succeeded in doing so, and in stained specimens have found the structure of the flagellates to be as follows: The round body takes a blue stain and the chromatin is arranged about the periphery in small clumps. From these clumps or chromosomes there are projected slender filaments of chromatin which occupy the center of a slender mass of protoplasm, derived from the protoplasm of the organism. This slender thread of chromatin enveloped in protoplasm constitutes the flagellum. Some flagella do not possess any chromatin, and in some the chromatin seems to be irregularly distributed.

Bastianelli* has demonstrated that in the free flagella the chromatin is collected at the center, the two extremities consisting of protoplasm. He is inclined to believe that the crescents

*"Lancet," London, 1898. Vol. II, p. 1620.

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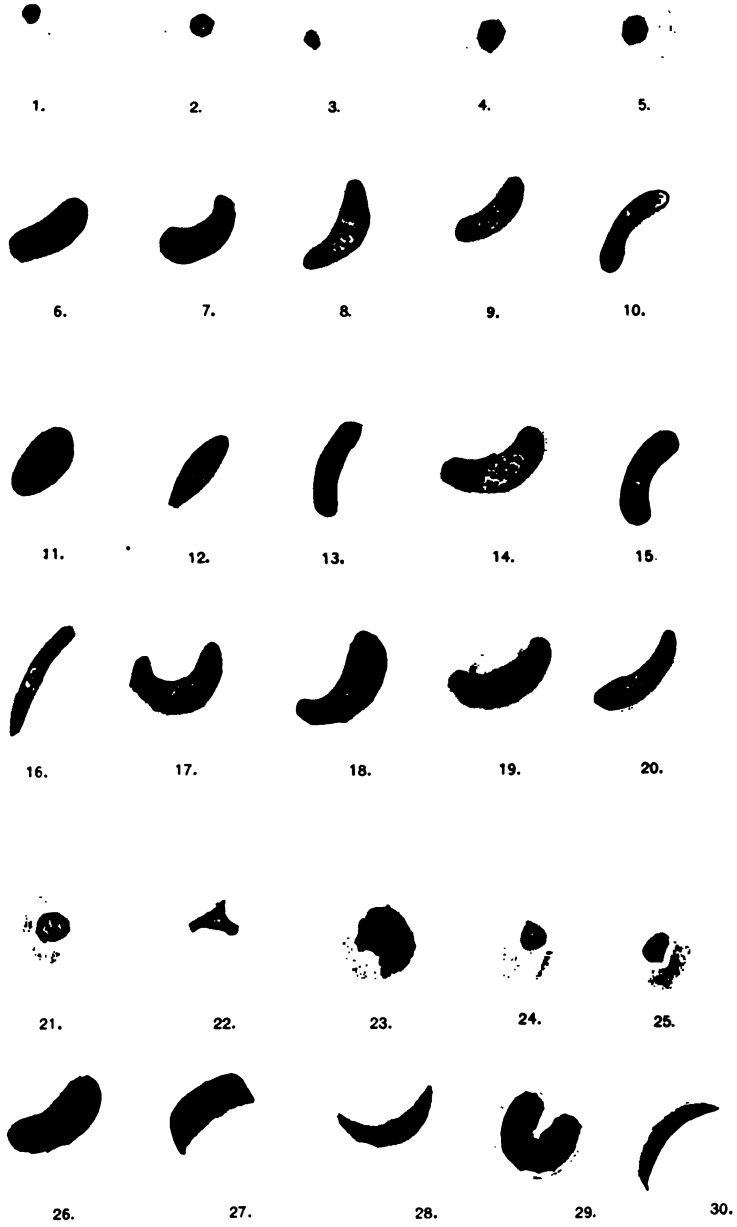
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PLATE II

STAINED INTRACORPUSCULAR AND CRESCENTIC FORMS OF THE ESTIVO-AUTUMNAL PARASITES

Note the polar staining of the crescents, the irregular staining of the protoplasm, and the eosin-stained border. Some of the crescents have lost the eosin-stained rim and stain almost uniformly throughout.



Craig, 1

Stained forms of the Estivoautumnal Parasites.

from which the flagellated bodies develop are sterile while they remain within the human body. The discovery of chromatin within the flagella of the malarial parasites adds another link to the conclusive evidence in favor of a life-cycle of the organism outside the human body, as it proves that they are living cells, and not, as was long believed, evidences of degeneration.

NOTE.—Ewing, in a recent article ("Journal of Experimental Medicine," March 25, 1901, p. 433), speaks very highly of the Nocht-Romanowsky staining method. This method as described by Ewing is as follows:

1. To 30 c.c. of polychrome methylene blue (Grübler) add five drops of a 3 per cent solution of acetic acid (U. S. P. 33 per cent).

2. Make a saturated (1 per cent) watery solution of methylene blue (Grübler), dissolving the dye by gentle heat. This solution should be at least one week old.

3. Make a 1 per cent solution in water of Grübler aqueous eosin.

The mixture is prepared as follows:

To 10 c.c. of water, add 4 drops of the eosin solution, 6 drops of the polychrome methylene blue and 2 drops of the 1 per cent methylene blue, mixing well. The preparations are stained for two hours, specimen side down. The best results are obtained after twenty-four hours.

Personally I have never used this method of staining, but it is undoubtedly a valuable one.

CHAPTER VII

ETIOLOGY—PREDIS

PREDISPOSING CAUSE.—The estivo-autumnal or re-demonstrated, hæmame-autumnal fever. These disease, but there are ment of the parasites w

These are known and considered here.

1. *Locality*.—A k malaria is most important infected can thus be malarial district is a p malarial fevers are of v said of the estivo-aut much more limited in northern latitudes, be approach the tropics.

In North America low regions of the southern Gulf states. It is common in its southern branches. Pacific coast, and no region of California. far north as Delaware pernicious forms occur

In South America mon, especially along Guiana, Brazil, Ecuador coast of Central America and here the very worst

In Europe, the south Crete, Italy, Venice, from this type of m

SECOND EDITION.

AN INDEX OF SYMPTOMS

As a Clew to Diagnosis.

By RALPH WINNINGTON LEFTWITCH, M.D.

Late Assistant Physician to the East London Children's Hospital.

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NEW YORK.

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toriously infected. People sleeping in the lower stories of houses
are more apt to become infected with malaria than those in the
upper stories. This fact was supposed to be due to certain low-

lying noxious vapors from malarious regions penetrating the lower more often than the upper floors of dwellings. The fact is easily explained when we know that the mosquito seldom flies to any height.

5. *Moisture*.—Marshes and damp regions are, as a rule, conducive to malaria, and moisture seems to be a most important factor in the distribution of the disease. Here again, the truth of the inoculation of the disease by mosquitoes is confirmed, for it is precisely in such places that mosquitoes are most numerous and breed most abundantly.

6. *Soil*.—Tropical jungles, low marshy lands, or lands covered with pools of stagnant water, are most apt to be malarious. This is not due directly to the soil, but is, as Marchiafava well says, "due to the fact that beneath a more or less thick stratum of humus there is an impervious layer" which gives rise to pools of water and general moisture of the soil. Such a soil favors the spread of the disease, as it brings about favorable conditions for the development of the infecting mosquitoes. As Marchiafava and Bignami say: "These conditions consist in the formation in the summer . . . of small collections of stagnant water covered with a layer of vegetation, surrounded by mud and shaded by rank vegetation. Now, in these stagnant pools, the larvæ and nymphæ of the mosquitoes, which infest the house of the wretched sufferers from the fever, find a suitable rest."

Turning up of the soil in places long undisturbed has often been followed by extensive outbreaks of malaria.

7. *Winds*.—Some authorities have considered that malaria could be transmitted by the winds, while others have regarded winds as being protective in their nature. The latter theory is probably correct, for as malaria is inoculated by the bite of the mosquito and as these insects do not fly about when the wind is blowing, it follows that the malaria is not transported by the wind.

8. *Rain*.—Rain favors the production of malaria because it favors the breeding of the mosquito. Added to this, rainy weather, by diminishing the resisting powers of the individual, favors the development of the disease in that individual after he has become infected by the mosquito.

Rains favor the breeding of the mosquitoes by giving rise to shallow, stagnant pools, which form ideal depositories for the eggs of the insect.

LOCAL PREDISPOSING CAUSES.—1. *Race.*—According to Thayer and Hewetson, the negro is less liable to contract malaria than the white man. As newcomers to a malarial district are much more liable to infection than old residents, it may be that the apparent immunity of the negro is only, in fact, apparent, for it should be remembered that it is the dark-skinned races which chiefly inhabit the most malarious countries.

2. *Age.*—Children are more susceptible to infection than adults. This is probably due, partly, as suggested by Marchiafava, to the fact that mosquitoes bite children in preference to adults.

3. *Sex.*—When equally exposed, both sexes have the same ratio of infection; but, as a matter of fact, malaria is more common in men than in women, as the latter remain at home more and are not exposed as often to the bites of the mosquitoes.

4. *Occupation.*—The occupation of man becomes a predisposing factor in the production of the disease in proportion to the chances that occupation gives him of infection. Laborers working at ditching, railway building, etc., which necessitate the turning up of the soil, are especially liable to attacks of malaria. An instance of this was the terrific mortality from estivo-autumnal fever during work upon the Panama canal.

OTHER PREDISPOSING FACTORS.—Anything which lessens the individual's resisting powers, such as sudden chilling, dissipation, overeating, privations, overwork—mental or physical—etc., is a predisposing cause.

CHAPTER VIII

ETIOLOGY (CONTINUED) DIRECT INFECTION—BY AIR—BY WATER —BY INOCULATION

THE malarial poison may, according to various observers, reach the human economy through three channels: by the respiratory tract, by the digestive tract, or through the skin by inoculation. The first two channels include the air and water theory of the transmission of the disease, and neither have sufficient experimental data to establish them. The last or inoculation theory is the only one which has been proved experimentally and is worthy of acceptance. Before considering it in detail a short review will be given the air and water theories.

1. TRANSMISSION BY AIR. — Until recently most authorities considered that malarial disease was transmitted by the air, which, in localities infected with malaria, carried the parasites, which were supposed to be present in the soil or water. Although accepted by many, this theory has never had a single experimental fact to uphold it.

To this theory we owe the common opinion that the air of malarious localities is poisonous; that the vapors and fogs arising from marshes or low rich lands are laden with malaria, and numerous other fanciful opinions, which, even though we now know them to be false, it will take years to efface.

It would seem that the most convincing argument against the transmission of malaria by the air is the fact that the disease is not conveyed by the wind, for it is impossible to suppose that if the malarial germ were present in the air it would not be carried by the winds.

2. TRANSMISSION BY WATER. — Numerous facts have been brought forward by the believers in the theory that water transmits the malarial poison, but all of them can be otherwise explained, and there is no experimental evidence to prove the truth of the theory. Large numbers of the experiments have been performed (all of which have ended in failure), to produce the dis-

ease by drinking water from infected places. Celli and Zeri have investigated this subject very thoroughly, and have come to the conclusion that malaria is never transmitted by the water of marshes or swamps. Their experiments were very carefully performed, and failed utterly to indicate that malarial fever was due to the drinking of water from malarious districts.

More recently Ross claims to have produced malaria in a human being by allowing him to drink water which contained the dead bodies of mosquitoes infected with the malarial parasite. He followed this supposedly successful attempt by others, but he was never afterward able to produce the disease; so that it is but reasonable to regard the first and successful attempt as merely a coincidence. It may be that malaria can be thus transmitted, but there certainly exists no valid reason to-day for such a belief.

3. BY INOCULATION, THROUGH THE SKIN, BY THE MOSQUITO.—This is the one method of infection which has been confirmed by abundant experimental evidence, and which, to-day, is accepted by all authorities, as the most common means of infection. Marchiafava and Bignami go even further and claim that the inoculation of malaria by the mosquito is the only way that the disease is transmitted. I believe, in the present rather dimly defined state of our knowledge, that such a statement is too radical, but am willing to admit that as far as we at present know, the theory of the inoculation of the disease by the mosquito is the only one which is worthy of our belief. In a most convincing manner Marchiafava and Bignami* refute the arguments of the air and water theories, and sum up in favor of the inoculation theory as follows: "Thus, admitting that malaria in man is the result of inoculation by mosquitoes, it is not difficult to explain why it is practically not carried by the wind; it is also easy to understand why the danger of acquiring malaria is greatest in the evening and the night. We see at once why the infection does not rise far above the ground; we comprehend readily the danger of sleeping in malarious districts; and finally, this theory explains perfectly the well-known prophylactic efficacy of mosquito nets in regions where malaria prevails. Also this agrees with what we know of the habits of mosquitoes in malarious countries, which sting especially at evening and during the night, do not fly far from marshes, or places where the proper

* "Malaria: Twentieth Century Practice," Vol. XIX, p. 111.

conditions of their existence prevail, are in hiding during the day out of the way of the winds, are most numerous in places where malaria prevails, disappear from places where works of sanitation have removed the conditions necessary to their existence, do not fly to any great height above the ground," and many other arguments.

Nuttall,* in an elaborate review of the evidence in favor of the transmission of malaria by the mosquito, mentions the following facts, which I have tabulated below:

1. *The Malarial Season.*

a. Corresponds to a period of warmth and moisture, conditions most favorable for the development of mosquitoes.

b. Develops after the first rains, which form pools in which mosquitoes multiply.

c. Malaria often ceases after excessive rains, when such pools are flooded and washed out.

d. Malaria is more prevalent in wet years, when mosquitoes are most numerous.

2. *The Malarial Country.*

a. Malaria is most common in low, moist countries, swamps, jungles, low seaboard, river deltas and valleys, and in such places mosquitoes most abound.

b. Malaria is most common as the equator is approached, and insect-life is also most abundant throughout the year.

3. *Conditions Affording Protection from Malaria and Mosquitoes.*

a. Protection of the body, as closing the windows and doors at night and using mosquito nets, gauze veils, curtains, etc. This has long been recognized by the inhabitants of malarial countries.

b. Thickly-built houses exclude malaria. Malarial fever seldom penetrates far into cities, as mosquitoes are stopped by walls, hedges, etc., and are attracted by the lights in the suburbs.

c. Intervening woods and expanses of water protect from malaria, the woods by obstructing the passage of the mosquito, acting as a sort of screen. Bodies of water are protective because the mosquitoes perish in them or do not try to cross them, as the mosquito is not capable of prolonged flight.

d. Cultivation of the soil: Malaria is prevented by cultivation of the soil, due to the fact that this destroys the stagnant pools and swamps, or "mosquito nurseries."

* Johns Hopkins Hospital Reports, Vol. VIII.

e. Flooding the land will prevent malaria by destroying the breeding-places of the mosquitoes.

f. Avoidance of sleeping out-of-doors at night or exposure after sunset: Mosquitoes bite mostly at night, and when asleep the person bitten does not know it, and thus is bitten often.

g. Use of fires: Fires indoors or out protect against malaria because the mosquitoes are attracted by them and fly into them and perish before reaching the person.

h. Immunity of persons working in sulphur mines: Due to the fact that the mosquitoes are repelled by the smell of sulphur.

4. *Influence of Occupation.*—The more exposed a person is, by occupation, to night air in malarious districts or to the soil, the more liable is he to contract malaria, as he is thus exposed to the bites of mosquitoes.

5. *Effect of Turning up the Soil.*—Malaria often follows excavations, etc., and it is probable that in such cases pools of water are formed in the excavated land, thus giving rise to fit breeding places for the mosquito.

6. *Elevation and Malaria.*—Malaria is most dangerous near the ground, and people living in the upper stories of houses escape. Mosquitoes fly low and the nearer the ground one is the more apt he is to be bitten.

7. *The Role of Insects and Ticks in Other Hematozoal Diseases,* as the mosquito in filariasis, the tick in Texas fever, etc. Reasoning from analogy this is presumptive evidence.

8. *The Coincidence of Malaria and Mosquitoes.*—Wherever malaria is, there are mosquitoes; but we do not always find malaria where we find mosquitoes, as the species of mosquitoes necessary may not be present.

From the above, it will be seen how strong is the presumptive evidence in favor of the inoculation theory of the disease, but we do not have to depend upon it to satisfy ourselves, for we have absolute experimental evidence which proves beyond all doubt that malarial fever is a disease inoculated into man by the mosquito.

To the brilliant work of Manson, Ross, Bignami, Bastianelli, Marchiafava, and Grassi the world is indebted for the elucidation of one of the most important etiological questions in medicine to-day.

I have already considered the development of the estivo-autumnal parasite within the mosquito, in a preceding chapter;

in view of the etiological importance of the inoculation theory, I shall quote in detail a portion of the experimental evidence showing that estivo-autumnal (remittent) malarial fever is inoculated by the mosquito.

Bignami was the first to succeed in producing estivo-autumnal fever through mosquito bites. His patient, one Sola, who had been an inmate in the Santo Spirito hospital for six years suffering from a nervous disorder, but who had never had malaria, offered himself voluntarily as a subject for experiment. The following is Bignami's record of the experiment. The mosquitoes used were from Maccarese, a very malarious district:

"Sola slept in the room in which the infected mosquitoes had been liberated from September 26 to the end of October, 1898. During the latter part of October the patient complained of malaise and headache. On the afternoon of October 31 he had a slight elevation of temperature to 37.2° C. [99° F.]. On November 1, at about 3 P. M., he was taken with a severe chill which lasted until five o'clock, the temperature rising rapidly to above 39° C. [102.2° F.]. Between nine and ten o'clock a feeling of cold was again experienced. The fever continued all night, falling in the early morning [November 2] to 38.2° C. [100.8° F.] and rising again that evening to 39.3° C. [102.7° F.]. The patient was restless and complained of very severe headache, but there were no grave symptoms. In the night, about eleven o'clock, he had another chill of short duration. During this night the temperature remained above 39° C. [102.2° F.], and on the morning of November 3 rose above 40.4° C. [104.7° F.], the patient being very restless and complaining of much suffering. The fever broke in the afternoon with a gentle perspiration.

"At quarter after five in the afternoon a hypodermic injection of one gram of quinine was given and again in the night. The fever fell, and at eight A. M. on November 4 the temperature was 36.7° C. [98° F.]. The administration of quinine was continued during the following days, the patient continuing to have slight elevations of temperature which did not reach 38° C. [100.4° F.] except once, on November 6. From November 7 onward the patient was entirely without fever, and rapidly regained his appetite and strength.

"An examination of the blood made with the greatest care on November 2 gave negative results, no malarial parasites being found. On the morning of November 3 a few young annular

parasites, motile and discoid, without pigment, and presenting the characteristic appearance of the parasites of estival fever, were found. These forms increased in number during the day, and were quite numerous during the afternoon hours. In some there was a beginning pigmentation at the border consisting of very fine granules of pigment.

"We see, therefore, that there was produced experimentally in Sola a grave malarial fever with a temperature curve such as is frequently seen in a primary estivo-autumnal infection. The fever began briskly, continued with slight remissions from November 1 to 3, and began to fall on the evening of the latter day when the specific remedy was administered. The parasites found in the blood belonged to the estivo-autumnal species.

"This is perhaps the first time that, in the primary estival infection acquired in the natural way, examinations of the blood have been made from the beginning of the fever. We find that after forty hours the parasites begin to be found, at first in small numbers, but rapidly becoming more and more numerous.

"According to the opinion of all who followed this experiment, it was conducted in such a way as to silence all objections. Sola is a robust individual, notwithstanding his nervous malady, who has never in his life had malarial fever, and who has not been outside of the Santo Spirito Hospital for six years. The room where the experiment was conducted was an annex of the San Carlo ward, in which, within the memory of the hospital physicians, there has never been an autochthonous case of malarial fever, nor has there ever been any malaria in the neighboring houses.

"Now in a room in the San Carlo ward of the Santo Spirito Hospital (Rome) Sola acquired a malarial infection produced by estivo-autumnal parasites, with a well-marked fever and symptoms so grave as to call for the prompt administration of quinine. The fever indeed was exactly such a one as is ordinarily caught by laborers in the Roman Campagna in the summer and autumn months, a fever beginning with the typical curve of the estivo-tertian or sometimes with a continued curve. This identical fever, such as prevails at Maccarese, was taken by Sola in a place when there was of Maccarese neither the water nor the air nor the soil, but the mosquitoes alone. We are then forced to the conclusion that the fever was acquired by inoculation by the mosquitoes."



While in this case there could be no doubt that the mosquitoes were responsible for the fever, it was not definitely settled just what species of mosquito was concerned, as there were three different species liberated in the room. After this experiment Grassi, Bastianelli, and Bignami worked with the *Anopheles Claviger*, and never failed to produce the disease when they were used. The following, a successful experiment performed by Bastianelli and Bignami, and quoted in their own words, is of great interest in many ways:

"A patient suffering from a relapsing estivo-autumnal infection, in whose blood were many crescents and round and flagellated bodies, slept, from December 10 to 18, in a room in which had been set free about fifty individuals of *A. Claviger*, brought from Maccarese. The temperature of the room was maintained at from 18° to 22° C. [64.4° to 71.6° F.]. Most of the mosquitoes stung the patient, and became infected with crescent bodies, and subsequent examination showed in the middle intestine the characteristic forms in process of development. But it was also observed that the mosquitoes remaining in the room at the given temperature during the last days of December did not have in the intestines mature sporozoa with sporozoites, but only the growing forms. Evidently at a temperature of from 18° to 22° C., the life-cycle of the parasite is completed very slowly. But these same mosquitoes, confined for a few days in an incubator at a temperature of 30° C. [86° F.], were found to contain forms of a later development. There were noted, enclosed in the intestines, typical capsules filled with sporozoites, and also broken and empty capsules, and in the salivary glands were numerous sporozoites.

"When this fact was noted, three mosquitoes of this group were kept in an incubator at 30° C. for two days, and on January 2 they were made to sting a new subject, A. R——, who lent himself knowingly and willingly to the experiment. It is needless to say that this man had never had malarial fever. On January 5 two of the same mosquitoes were made to sting the same person again, who then had been stung in all five times by three specimens of *A. Claviger*.

"After this part of the experiment, the three mosquitoes were dissected and examined under the microscope, with the following results: '*A. Claviger*, No. 1. In the intestines were found very many capsules with sporozoites, and some capsules which had

been ruptured and completely emptied of their contents. In the salivary glands were found two infected tubules; in one were seen the cells swollen, of ovoid form, and filled with granules of uniform size. When pressure was made on the preparation there issued a very large number of sporozoites of typical form, uniform in appearance, and all of equal length; in the other tubule were also seen cells containing filiform sporozoites of characteristic appearance.'

"*A. Claviger*, No. 2.—In the intestine were very numerous capsules, some still whole and filled with sporozoites, others ruptured and shrunken, and containing a granular residuum of a pale yellow color. In some of these, ruptured capsules were seen, also brown bodies of various size and shape, some elongated, others short and deformed. In the salivary glands all the tubules were infected except one or two. In them were seen cells containing typical sporozoites, cells filled with granules similar to those described in the case of *A. Claviger*, No. 1, and cells filled with round hyalin bodies of variable size. In addition there were also found typical filiform sporozoites along the excretory ducts of the gland.'

"*A. Claviger*, No. 3.—The intestine was filled with mature sporozoa. Many capsules were broken and shrunken, and contained a pale yellow detritus; others contained a large central body of granular aspect, surrounded by a hyalin halo and without any recognizable structure. These were possibly mature sporozoa in process of degeneration. The salivary glands were not found infected. From the results of these examinations we may conclude that of the three specimens of *A. Claviger* employed, only two had inoculated the patient with malaria.'

"On the evening of January 10 the patient had a sense of heat and a headache, but the temperature was normal. On January 11, 12, and 13, there was no fever and the patient felt well. On January 14, that is, after from nine to twelve days' incubation, there was no fever until eight o'clock in the morning, but then the temperature began to rise rapidly and reached 39.5° C. [103.1° F.] at noon. From this time the fever remained continuous up to January 18. The temperature fell to normal at six in the morning of the 18th. [Two grams of quinine were given hypodermically on the 16th, and repeated on the 17th, and recovery was complete and rapid.]

"On examination of the blood on the morning of January 16

there were found scanty estivo-autumnal parasites with very fine pigment-granules at the periphery. There were found, also, plasmodia without pigment and with granules, in normal red blood-corpuscles and in brassy bodies. The parasites disappeared after the exhibition of quinine on January 17. Thus the infection was rapidly cut short and no crescent bodies were seen.

"We have in this case a typical example of estivo-autumnal infection, beginning with a continued fever, as is usual with this group of malarial infections. The course of the disease was in every respect identical with that in the first case of malarial fever experimentally induced by the stings of mosquitoes [the Sola case described by Bignami]."

From the above it will be seen that the disease was caused by the bites of only two insects, and, as pointed out by Marchiafava, this is not surprising when one considers the vast number of sporozoites in the infected salivary glands of a single mosquito. There is no reason to doubt that one mosquito might infect a number of individuals. From the experimental evidence which has accumulated, of which I have only given a small portion, we must conclude that estivo-autumnal malarial fever, and in fact, all malarial fevers, are produced in man by inoculation through the bite of certain species of mosquitoes, and while it cannot yet be proven that this is the only manner of infection, it is but reasonable to suppose that such is the case.

The most striking recent confirmation of the mosquito theory is found in the experiments of Sanbon and Lowe. These investigators spent an entire summer in the most malarious portion of the Roman Campagna, residing in a mosquito proof hut. During the day the time was spent mostly out of doors, but at evening and during the night the time was spent indoors. Neither investigator developed malaria, although many individuals residing in the same locality, without protection from mosquitoes, suffered severely from the disease.

CHAPTER IX

TRANSMISSION BY INOCULATION FROM MAN TO MAN—INCUBATION—IMMUNITY—SPONTANEOUS RECOVERY

TRANSMISSION BY INOCULATION FROM MAN TO MAN.—I have, in a previous chapter (Chapter V), considered this method of the transmission of estivo-autumnal fever, and from the experimental data there given two facts are demonstrated, viz.:

First, that the malarial fevers may be transmitted to a healthy individual by the inoculation of blood from an individual suffering from the disease.

Second, that the type of fever inoculated is always reproduced in the individual—that is, if a healthy individual is inoculated with blood containing the tertian malarial parasites, tertian fever will follow; if with blood containing the estivo-autumnal parasites, estivo-autumnal fever will follow, etc.

Such inoculation experiments also prove that the mosquito is not absolutely necessary to the transmission of the disease experimentally; but it is doubtless a fact that it is essential in nature, and it certainly is in the extra-corporeal cycle of existence of the malarial parasites.

INCUBATION.—Much has been written as to the period of incubation of the malarial fevers, but I will only consider here that phase of our subject which relates to the incubation of the estivo-autumnal fevers.

The period of incubation is the time elapsing from the infection of the individual with the parasite to the first clinical symptoms of the disease. Obviously this is often a very difficult point to determine, and it is only occasionally that one can be sure of his data upon the subject. Hertz believes that the incubation varies from six to twenty days, and I am sure, from personal observation, that the incubation period can be even longer than twenty days. Some authorities have claimed, upon entirely insufficient data, that only a few hours may elapse from infection to the outbreak of the disease; but all experience is absolutely negative of such an opinion. As far as I know, the most satis-

factory datum which we possess upon the question of the incubation of the estivo-autumnal fevers is that given by Marchiafava and Bignami, who were so fortunate as to observe three cases in which they were certain of the time of infection. These cases are here given in these authors' own words:

"*Case I.*—A robust young man, twenty-five years of age, living in the central part of Rome, had never had malarial fever. On November 4, 1894, he was obliged to go to Sermonetta, a notoriously malarious town near the Pontine marshes. He arrived in the city at ten o'clock, slept that night, tormented with swarms of mosquitoes, in a house on the outskirts of Sermonetta, and in the morning returned to Rome, where he resumed his usual occupation. For six days he was in good health; then he had two days of malaise and on November 13, that is to say *nine days* after his stay in Sermonetta, he was taken down with an estivo-autumnal tertian fever, the parasites of this form being found in the blood.

"*Case II.*—An engineer, living in Rome, who had never suffered from malaria, was constrained by the duties of his calling to pass a day, in October, 1895, in a place in the Pontine marshes, and he slept that night in a cabin in poor repair in which were many mosquitoes. At the end of *ten days* an estivo-autumnal infection, with irregular fever, developed, of which he had several relapses, extending up to the following spring."

"*Case III.*—A lady who for many years had enjoyed good health passed a week at Fiumicino in the month of October, 1894. Three days after her return to Rome an estivo-autumnal malarial fever declared itself, and, not being promptly treated, developed into a choleraic pernicious attack; following this the patient remained profoundly anemic, with a sanguinolent diarrhea, and died at the end of a few weeks."

From the above cases it will be seen that the period of incubation was from nine to ten days.

Much data have been collected regarding the incubation period from the inoculation experiments, and I have given the most important.

Bastianelli and Bignami found in estivo-autumnal fever the maximum period of incubation was five days, the minimum two, mean three days; Bignami, maximum ten, minimum six.

Mannaberg, seven cases, three to fourteen days, mean six and a half; Marchiafava and Bignami, maximum fourteen days, minimum two, mean six and one-tenth days.

All these observers have found that the greater the amount of infected blood inoculated, the shorter was the period of incubation.

The chief fault with the above data is that it was obtained by the inoculation of the disease in an unnatural manner. We know to-day that malaria is due to the inoculation of sporozoites from the mosquito into man. In the inoculation of blood containing only the forms of the parasite belonging to the human cycle it is reasonable to suppose that the period of inoculation will be shorter than is the case when the mosquito transmits the sporozoites to man, and that it is so has been proved experimentally, for Marchiafava and Bignami have found that an individual stung by mosquitoes which had sucked blood containing crescents developed estivo-autumnal fever in from nine to twelve days, almost the exact period observed in the cases quoted, where infection occurred in malarious localities. But though the period of incubation of these fevers is doubtless, for the great majority of cases, from nine to twelve days, cases do occur which show a much longer period of incubation, sometimes of weeks or months. Sternberg quotes the cases of certain sailors who were infected while their ship lay two days in port, and who developed the disease, one after forty-eight, the other after one hundred and eighty-four days after leaving the port. I am fully convinced that estivo-autumnal fever may have a very long period of incubation, and in support of this fact may mention the following personal experience:

A surgeon of the United States Army, August, 1899, was in camp outside of Havana, Cuba, in a malarious district. In September he returned to New York, and then was ordered to San Francisco. From August, 1899, until March, 1900, he enjoyed good health, but during March he suffered from general malaise and a chronic diarrhea. On April 1 he had a slight chill and his temperature rose to 106.2° F. His blood showed numerous ring-forms and pigmented forms of the estivo-autumnal parasites, and though this attack was quickly overcome by quinine, he has had several relapses since.

In this case I am convinced that his infection occurred while in camp at Havana, for the reason that estivo-autumnal fever is not present in New York city or San Francisco, and he was in no other places than these after coming from Havana. In this case, then, the incubation period was at least seven months.

As to the explanation of such long periods of incubation, I believe the theory advocated by Thayer to be the true one, i. e., that the parasites multiply and perform their life-cycle, but in such small numbers that they give rise to no observable clinical signs. I am the more convinced of this, as it is borne out in the examinations of blood in cases of soldiers returning from the tropics. In the United States General Hospital at San Francisco the blood of every case admitted is examined for the malarial parasites, whether or not clinical symptoms are present. This routine practice has led to the surprising discovery that at least 40 per cent of the cases whose blood contains the malarial parasite have no clinical symptoms of the disease, and a large proportion of these cases show the estivo-autumnal parasite to be present. Many of these cases have shown the parasites for weeks, and the life-cycle in the ordinary tertian cases followed, in small numbers, with no clinical symptoms present; and I consider that this proves beyond all doubt the truth of Thayer's theory and shows conclusively the reason for long periods of incubation. It is not too much to say, that if this routine method of examining the blood of every patient in malarious districts, or coming from such districts, could be followed in every hospital, our ideas regarding the relation of malaria to other diseases would be greatly modified. I shall discuss more thoroughly this subject in the chapter devoted to the diagnosis of estivo-autumnal fevers.

The question arises, How long will the susceptible individual live in a malarious country before acquiring the disease? It is impossible to answer this question for all cases; but in the great majority of instances an individual residing in a region infected by estivo-autumnal fever will acquire the disease in from three weeks to two months, provided he is exposed. Of the hundreds of cases of malaria occurring in our soldiers in Cuba, almost 95 per cent gave a history of being there for from two to six weeks before the onset of the disease. One month was the most common period given by the men as intervening between landing in Cuba and the first chill.

As in many other diseases, the length of the period of incubation varies with the amount of the infecting agent, the physical condition of the infected individual and his surroundings, as regards exposure, hardship, heat and cold, insufficient nourishment, etc.

IMMUNITY.—Immunity to estivo-autumnal fever undoubtedly

exists, and such immunity may be considered under the following divisions: Racial immunity, congenital immunity, and acquired immunity.

Racial Immunity.—It has been said that certain races of mankind are immune to the malarial fevers. This statement is undoubtedly false and cannot be proved by facts. While this is so, it is a well-recognized fact that some races are more resistant to malaria than others. The black races are relatively immune to the disease, but the immunity is undoubtedly acquired. Plehn has demonstrated that the Kamerun negroes rarely have malarial fever, and generally recover spontaneously; whereas Europeans suffer very severely in the same locality. The same is said of the Malays by Martin, while Tommasi-Crudelli has noticed differences in the resisting power of the inhabitants of certain localities of Italy.

While such differences in the susceptibility to malaria undoubtedly exist, they may all be explained by the theories of acquired immunity, and it is true that no people inhabiting the world are, as a race, immune to the malarial diseases.

Congenital Immunity.—There undoubtedly exist many people, living in the most malarious localities, who have never suffered from the disease, and to them we must accord the fullest degree of immunity. This immunity is in all probability congenital, and has even been proved, in a few instances, to be a family characteristic.

Acquired Immunity.—Long residence in a malarious country will, undoubtedly, if the individual survives, confer upon him a relative immunity to the disease. As is the case with other diseases, repeated attacks of malaria in man will, in time, render him less liable to further attacks. In other words, the malarial poison produces certain changes in the human organism which render it at least partially immune to future attacks. This immunity, however, is often gained at the expense of the vitality of the individual, and the penalty inflicted is a chronic malarial cachexia, which markedly lowers the health of such so-called immunes. The history of acquired immunity is simply that of repeated attacks of the malarial fever, each one a little less severe than the preceding, until at last a spontaneous cure is effected.

The immunity thus acquired may be lasting, but, as a rule, unusual hardship, privation, ill health or removal to a new locality will destroy it, and he who thought himself immune learns by

sad experience that absolute immunity to the malarial fevers is so rare as to be almost non-existent.

SPONTANEOUS RECOVERY.—It would seem well in connection with immunity to review the question of spontaneous recovery from the estivo-autumnal fevers. By spontaneous recovery we mean the dying out of the infection without the intervention of medicines. In the pre-quinine days this was the way in which most malarial affections were cured, and, as often happens, the physician received the credit due to nature. To what, then, when spontaneous recovery occurs, is it due? No one knows exactly, but some deductions can be drawn from the examinations of the blood in such cases, and the known facts regarding this termination in the disease.

In the first place, examination of the blood in cases which are undergoing spontaneous recovery shows a gradual diminution in the number of parasites present. Together with this diminution, which is progressive, certain degenerative changes are noted, such as vacuolation, fragmentation, etc., of the matured organisms. Numerous pigmented leucocytes and much free pigment are also often found. Many times, in cases recovering spontaneously, the entire life-cycle of the parasite may be followed in the blood, in tertian or quartan fever, but they are so few in number that no clinical symptoms are produced. I have repeatedly observed this fact.

Metchnikoff and his adherents have laid much stress upon the relation of phagocytosis to spontaneous recovery, but there are no experimental data or observations sufficiently convincing to prove the phagocytic theory. I have already considered the subject of *phagocytosis* as it is related to estivo-autumnal fever, and although it is doubtless a factor in the process of spontaneous recovery, it is certainly only a secondary one. It must, I think, be admitted that the phagocytic cells, by destroying a certain number of parasites and removing from the blood large quantities of pigment and excrementitious matter, help in producing recovery from the infection, but phagocytosis, *per se*, is not the cause of spontaneous recovery.

The question arises: To what is due the degenerative changes noted in the parasites in cases undergoing spontaneous recovery? Mannaberg believes that the fever present is detrimental to the growth of the parasites; but this can hardly be so, for often cases showing the highest temperature present large numbers of

parasites in the blood, all of them in normal condition. Marchiafava leans to the theory that in malaria, as in bacterial diseases, the parasite gradually loses its virulence. In opposition to this it may be urged that the cause of malaria is not a bacterium, but a parasite belonging to the animal kingdom, totally different in its structure and life-history, and that there is absolutely no evidence of such diminution of virulence. Personally, I do not believe that the argument of diminished virulence can be applied in this case, as even in bacteria such diminution does not lead to disintegration. If, then, neither the fever nor the theory of diminished virulence hold good, as explanations of the death of the parasites, to what is their degeneration due? In answer, I would say: to certain antitoxic substances elaborated by the white cells and excreted, and to others liberated by the breaking down and disintegration of the leucocytes.

It is an established fact that some of the white cells, especially the eosinophiles, excrete certain substances which are very destructive of parasitic life, and what is more natural to suppose than that these antitoxic materials, as they may be called, are prejudicial to the development of the parasites of malaria. This excretory function of the leucocytes is, in my opinion, far more important in the production of spontaneous recovery than is phagocytosis. As a matter of fact, phagocytes are often more numerous in pernicious cases, resulting fatally, than in mild cases, whereas the coarsely granular oxyphile or eosinophile is always more numerous in mild cases than in severe ones, and is very often very largely in excess in the cases undergoing spontaneous recovery. As a rule, in estivo-autumnal fever, the appearance of crescents in the blood is coexistent with the spontaneous disappearance of the clinical symptoms and the intracellular parasites. It would seem from this that the life-cycle of the parasite within the human body had ceased, the extra-corporeal form of the parasite having been produced. Certain it is that the appearance of crescents and the disappearance of other forms of the parasites denote spontaneous recovery from the disease.

To sum up, then, the causes of spontaneous recovery, I would place them in the following order, as regards their importance:

1. Production and excretion of certain substances, bactericidal and antitoxic in nature, by the coarsely granular oxyphile or

eosinophile, which substances cause the death and degeneration of the parasites of malaria.

2. Disintegration of the leucocytes and liberation of certain antitoxic and bactericidal substances, having a similar action.

3. Phagocytosis, i. e., the engulfing and digestion of the parasites. All these processes, without doubt, occur simultaneously, and to them is due, I believe, the spontaneous cure of the disease.

Often, however, spontaneous recovery is more apparent than real. The fever may disappear, together with many or most of the clinical symptoms, only to be followed in a week or ten days by a relapse. Often, also, after spontaneous recovery seems to have occurred, an examination of the blood will demonstrate the presence of a few estivo-autumnal parasites, and these may persist for days and even weeks without causing any noticeable symptoms. Again, the parasites may entirely disappear from the peripheral blood, but blood obtained by puncture of the spleen will show numerous parasites in all stages of development.

Indeed, a sharp distinction should be drawn between apparent and real recovery in the estivo-autumnal malarial fever, and personally, after a large experience with these fevers, I am convinced that it is impossible to say when a patient is actually cured, for relapses occur so frequently that a guarded statement concerning cure is always advisable.

CHAPTER X

GENERAL PATHOLOGY OF THE ESTIVO-AUTUMNAL FEVERS— CHANGES IN THE RED CORPUSCLES—MELANEMIA—ANEMIA— THE URINE—THE ETIOLOGY OF THE FEVER.

PATHOLOGY OF THE BLOOD.—The pathological changes which occur in the blood as the result of estivo-autumnal infection are due to primary and secondary causes. The primary cause is the infection of the red cells with the parasites and the changes brought about by such infection; the secondary is the anemic condition, which is the inevitable result of malarial infection.

THE PRIMARY CHANGES IN THE BLOOD.—These changes are brought about by the invasion of the red cells by the estivo-autumnal parasites. The chief are:

Changes in Form.—Red corpuscles invaded by the estivo-autumnal parasites are generally smaller than normal, and often appear shrunken and wrinkled or crenated. This is especially true of those infected with the quotidian estivo-autumnal parasite.

Changes in Color.—Such infected corpuscles are often a very dark olive-green in color and present a brassy appearance. This change is also most marked when the corpuscles are infected with the quotidian parasites. These "brassy bodies" are most numerous after a paroxysm, when the parasites have reached the pigmented stage, and are also more numerous after the administration of quinine. This change is thought to be, by most authorities, due to a necrosis of the infected red cell.

Retraction of Hemoglobin in Infected Corpuscles.—Many infected red corpuscles show a retraction of the coloring matter at some portion of their periphery, small areas being entirely colorless. Often the hemoglobin membrane, as it may be called, is retracted about the contained parasite, and this is notably so in the case of crescents, which often appear as though enclosed within a thin greenish web. It is to this change in the red cell that the "bib" and double outline of the crescent is due.

PHAGOCYTES.—The occurrence of pigmented leucocytes and phagocytes has already been discussed.

MELANEMIA.—The occurrence within the blood, either free or within leucocytes, of malarial pigment, is known as melanemia. This pigment may be brown, brownish yellow or black in color, and may occur as blocks, granules, rods, grains, irregular clumps, fine needles, or cylindrical, polyhedral, circular or irregular masses. This condition is only present in malaria, and is often of great service in diagnosis where the parasites are few in number or in chronic malarial poisoning.

Historical.—It would be unprofitable here to enter fully into the history of the many observations which have been made upon this subject, but a short résumé will be given of the most important.

Meckel,* in 1847, was the first to describe pigment occurring in the blood, and his observations were confirmed by Virchow† and Frerichs. All of these investigators considered that the pigment was from the spleen or liver, Frerichs believing it to be from the spleen only.

Meigs and Colin wrote very excellent descriptions of the condition, but to Arnstein‡ we owe the discovery that the pigment arises in the circulating blood. Arnstein's theory is as follows: During the fever the red cells are destroyed and the pigment formed is liberated and taken up by the leucocytes and deposited in the tissues.

Kelsch§ studied the subject very thoroughly, and came to the conclusion that the destruction of the red cells gave rise to the pigment which remained in solution in the blood until it became saturated, when it was precipitated in granules which were then engulfed by leucocytes.

Laveran, Marchiafava, and Celli|| demonstrated that the pigment is not formed after the disintegration of the red cells, but is formed during the growth of the malarial parasites, within them; being, in fact, the changed hemoglobin of the corpuscles, which has been absorbed by the parasites during their growth.

Two varieties of pigment are present in estivo-autumnal fever: one, *melanin*, or black pigment, present both in the blood and tissue; the other, *hemosiderin*, or yellow pigment, present only in the tissues. The first gives no reaction for iron; the second does.

*"Zeitschr. f. Psych.," 1847, p. 198.

†Virch. Archiv, 1849, 11, 537.

‡Virch. Archiv, 1874, Bd. lxi, 494.

§"Arch de Physiologie," Second Series.

||"Commentaria clin. de Pisa," 1879.

As regards the origin of the two varieties, I am fully in accord with Bignami, who says: "The melanemia, index of an acute infection, is derived only from the direct transformation of hemoglobin into melanin through the action of the parasites within the red corpuscles, as Marchiafava and Celli have demonstrated; that the melanosis of the viscera, spleen, liver, bone-marrow, etc., index of a previous infection, has a double origin. In chief part it is derived from the melanemia, that is, from the deposition in the viscera of the black pigment formed during the acute infection in the circulating blood; in part it has a local origin, that is, it is derived from the slow transformation of the blocks of ochre-colored pigment which are deposited or formed in the spleen and in the other viscera from the enormous quantity of altered red blood-corpuscles, which, in grave infections, die before the direct action of the parasites has transformed their hemoglobin into black pigment."

Chemical Characteristics of Melanin. (The Black Pigment.)—The pigment is decolorized by the potassium and ammonium salts; is soluble in sulphide of ammonium and insoluble in the strong acids.

No trace of iron has ever been demonstrated in it, but this does not, by any means, prove that it is not present. In all probability, melanin is closely allied to hematin, as is held by Carbour.

Distribution of Melanin.—The melanin formed from the hemoglobin of the red cells during the growth of the parasite is, after its segmentation and the destruction of the red cells, liberated in the blood-plasma, when it is taken up by the leucocytes and deposited in certain tissues, especially the brain, liver, and spleen.

The Yellow Pigment.—There occurs within the tissues (never in the blood) in cases of estivo-autumnal fever, a large amount of a golden yellow pigment, which is scattered throughout the tissues of the liver, spleen, and bone-marrow. It occurs as very fine grains, larger masses of an amber color, and as large blocks of a golden yellow color. This pigment arises from the hemoglobin of the red cells also, and has been called by Neuman* *hemosiderin*. This pigment is especially abundant in fatal cases of pernicious estivo-autumnal fever and occurs chiefly in the liver and spleen.

* Virch, Archiv, Bd. cxxi, p. 318.

Chemical Characteristics of Hemosiderin. (The Yellow Pigment.)—It is insoluble in strong acids, caustic potash, water, and alcohol; turns black when treated with sulphide of ammonium, and gives a blue color when treated with ferrocyanid of potassium, which is characteristic of hemosiderin. It will be seen that this pigment, unlike melanin, gives an iron reaction.

Distribution of the Yellow Pigment. (Hemosiderin.)—This pigment is present only in the tissues, and is most abundant in the liver and spleen. In the liver it is present mostly in the hepatic cells, unlike melanin, which is never found within these cells. In the spleen it is found within the cells or lying free in the splenic sinuses.

THE ANEMIA OF ESTIVO-AUTUMNAL FEVERS.—In all forms of estivo-autumnal fever there is a reduction in both the red and white blood-corpuscles. This reduction is more marked than in the ordinary intermittent fevers, and is due to the action of the parasites upon the corpuscles containing them; the action of poisonous material elaborated and set free by the parasites, and to inhibited function of the blood-producing glands, due to the changes brought about in them by the malarial disease.

The greatest factor in the destruction of the blood-cells is undoubtedly the direct action of the estivo-autumnal parasites.

The Red Corpuscles.—Kelsch* has investigated the subject very thoroughly, and has found that a reduction in the number of red cells follows every paroxysm; but it has also been found that *during* the paroxysm they may be increased. This reduction may be very great, Kelsch having observed only 500,000 to the cubic millimeter. In ordinary cases, after the fever has continued two or three days, the red cells will often fall to 2,000,000 or less per cubic millimeter. A peculiar fact about the anemia is, that while during the first few days the reduction of red cells is marked, the continuance of the disease, after a certain amount of anemia has been produced, is not characterized by a further reduction, there being no progressive falls. This is true in the majority of cases, but not in all.

In the pernicious forms of estivo-autumnal fever the reduction in red blood-cells is very rapid, a fall to 1,000,000 per cubic millimeter being often observed in twenty-four hours. If, however, the patient has suffered before from malaria, and is already anemic, the reduction is less, averaging a loss of about

*Archiv. de Physiologie, 1875, 690.

1,000,000 in the twenty-four hours. It must not be supposed, however, that all cases of pernicious malaria show so great a reduction in the red corpuscles.

The return to the normal number of the red corpuscles is generally rapid after a mild or even severe infection which has been promptly stopped by treatment; but cases untreated, or in which many relapses have occurred, are followed by a chronic and persistent anemia, which is one of the most marked characteristics of people inhabiting malarial regions. Dionisi* has contributed some very valuable data concerning the anemia of the estivo-autumnal fevers, and his conclusions are here given:

(In one case under my own observation the red cells fell to 690,000 per cubic millimeter, in three days, but increased to 2,100,000 per cubic millimeter in about three weeks, after treatment.)

"1. In estivo-autumnal fever, the reduction in the number of red blood-corpuscles bears a direct relation to the number of organisms. Where the parasites are numerous there is a constant reduction of from 200,000 to 1,000,000 with each febrile paroxysm; where the parasites are scanty the reduction is less.

"2. When crescentic bodies are present in addition to the other forms, they seem to exert no influence on the blood-changes.

"3. When, after a paroxysm, the number of corpuscles has suffered a sudden and very marked diminution, the succeeding paroxysms may be followed by but a slight reduction only, or even by an increase.

"4. In relapses, the reduction per paroxysm is less than in a primary infection.

"5. In infections determined by the amoeboid forms (acute estivo-autumnal infection) there is, during apyrexia, no complete return of the red corpuscles to their normal number. Some attempts at restitution may be seen during the first several days of apyrexia, while after this, during perhaps eight to fifteen days, there may be a steady reduction of from 100,000 to 500,000 red blood-corpuscles without the appearance of any parasites in the blood.

"6. Only after marked and continuous reductions following each paroxysm does there occur in the afebrile period a relative restitution of the red blood-corpuscles; this may be slow or rapid.

*Lavori del III Congress d

Milan, Oct., 1890, page 169.

"7. If the increase in the corpuscles has begun, the presence of crescents has no deleterious effect.

"8. In tertian and quartan fevers the same changes are observed, excepting that in the afebrile period there is a rapid and almost complete restitution of the red blood-corpuscles.

"9. The colorless corpuscles follow the same course as the red, both in apyrexia and fever. In later periods, however, when the red corpuscles have increased, there may still be a marked diminution in the colorless element.

"Bastianelli noted the association of the anemia of cachectics with actual changes in the marrow produced by the infection."

The White Corpuscles.—It may be said in general that the reduction in the white corpuscles, or leucocytes, corresponds with that of the red. During the paroxysm there is an increased number of leucocytes in the peripheral blood, while between the paroxysms they are very markedly decreased. They are always diminished in number relatively to the red corpuscles, and this is especially true of the blood of patients suffering from chronic malarial poisoning. The reduction in the leucocytes is observed in all cases of simple tertian or quotidian estivo-autumnal fever; but the reverse is true of cases of pernicious estivo-autumnal fever, in which they are very often greatly increased. Kelsch has observed as high as 35,000 leucocytes per cubic millimeter in the pernicious infections. In one case of fatal comatose pernicious estivo-autumnal fever which I observed, the leucocytes were very greatly increased, averaging at least one to every one hundred and twenty red corpuscles. This marked increase in the number of leucocytes in pernicious malaria is a strong argument against the theory, advocated by Metchnikoff and his adherents, that the leucocytes play the most important rôle in the spontaneous cure of the malarial fevers.

Reduction of Hemoglobin.—Besides the reduction in the red and white corpuscles, there is generally a marked reduction in the hemoglobin, in the estivo-autumnal fevers. This subject has been thoroughly investigated by Rossoni,* whose conclusions are here given :

"1. No acute infection results in as active a deglobulization as does malarial fever.

"2. In all cases of malarial fever there is an immediate diminution in the number of corpuscles and the amount of hemo-

*"Lavori del congresso società di medicina interna," Rome, Oct., 1889, p. 121.

globin. This loss generally bears a direct relation to the duration of the infection. In pernicious cases, however, a diminution of as much as two-thirds of the total amount may take place in from one to three days.

"3. The gravity of pernicious cases does not always bear a direct relation to the extent of the loss in hemoglobin.

"4. The destruction of hemoglobin and corpuscles bears, generally, a direct relation to the number of parasites in the blood. Occasionally, however, cases with high fever and marked losses in hemoglobin and corpuscles may show but few parasites in the circulating blood. A long-continued diminution of hemoglobin is often associated with the presence of crescents.

"5. The loss in hemoglobin and corpuscles is rarely evident during the paroxysm, but begins with apyrexia and may continue for several days afterwards.

"6. Recovery from malarial anemia is slower than from the other acute anemias.

"7. Usually the hemoglobin and corpuscles are equally diminished, but sometimes the hemoglobin is a valuable point in differential diagnosis between malarial fever and enteric fever or pneumonia.

"8. The restitution of the hemoglobin in malarial anemia is often incomplete, and individuals living in malarial districts have often a slightly smaller percentage of hemoglobin than those living elsewhere."

Post-Malarial Anemia.—In the majority of patients suffering from repeated attacks of malarial fever, of the estivo-autumnal variety, in whom a cachectic condition is present, there is present a greater or less degree of anemia, the red blood cells seldom numbering over 3,000,000 per cubic millimeter, and often not over 1,500,000 per cubic millimeter. In severe cases nucleated red cells are sometimes seen, and poikilocytosis is often present. In these cases the leucocytes and lymphocytes are relatively increased, while the polymorphonuclear leucocytes are decreased.

From their researches Dionisi and Bignami* have separated four types of post-malarial anemia, as follows:

"1. Anemias in which the examination of the blood shows alterations similar to those observed in secondary anemia, from which they differ only in that the leucocytes are diminished in number. The greater part of these cases go on to recovery; a

*"Cent. für allg., Path., u. Path., Anat.," 1894, v. No. 10, p. 422.

few, without any further change in the hematological condition, pursue a fatal course.

"2. Anemiæ in which the examination of the blood shows alterations similar to those seen in pernicious anemiæ—presence of giantoblasts. These cases end fatally.

"3. Anemiæ which are progressive, as the result of compensation by the marrow for losses brought about by the infection. At autopsy the marrow of the long bones is found to be wholly yellow, while the marrow of the flat bones is also poor in nucleated red corpuscles.

"4. Chronic anemiæ of the cachectic, which differ from the above-mentioned types by clinical and anatomical characters, in that the special symptoms of malarial cachexia prevail, while one observed post-mortem, a sort of sclerosis of the bone-marrow. The marrow of the long bones is red and many are necrotic; the nucleated red blood-corpuscles are very rare, and the colorless polymorphonuclear corpuscles are present in small numbers."

There is some difference of opinion as to whether or no the decrease of leucocytes, noted in acute paroxysms, is absolute or only apparent. Marchiafava and Bignami say regarding it: "In our opinion, therefore, leucopenia during an acute infection does not depend upon a real diminution in the number of leucocytes, but upon a change in their distribution caused by the tendency of the white cells to accumulate in the vascular areas in which the blocks of pigment, mature parasites, etc., in short, the substances which they take up, accumulate."

However this may be, the fact remains that the estivo-autumnal fevers are never accompanied by a leucocytosis unless that leucocytosis be due to some complication, as pneumonia.

THE URINE IN ESTIVO-AUTUMNAL MALARIAL FEVER.—In all forms of estivo-autumnal malarial fever the urine shows a greater or less number of pathological conditions to be present. The urine in this class of cases has been very thoroughly studied by Rem-Pici,* and to him we owe most of our knowledge concerning the changes which occur.

Amount.—As a rule, during the acute attacks of estivo-autumnal fever, the amount of urine is diminished. During the paroxysms the amount of urine passed is increased, but is diminished during the apyrexial stage. I observed recently an interesting case in which the patient recognized the impending

* "Politecnico Roma," 1893, I, p. 131.

occurrence of the paroxysms by the greatly increased amount of urine which he passed. In rare cases the greatest amount of urine is passed after, instead of during, the attack.

Polyuria.—While in the tertian and quartan fevers convalescence is often marked by the occurrence of polyuria, this is not so true of the estivo-autumnal fevers. A slight polyuria is, however, very common, and is probably much more so than is generally known. Now and then a very marked polyuria will be observed, as in a case observed by me, following a tertian-autumnal attack, in which for weeks the patient passed from 20,000 to 25,000 cubic centimeters of urine per day.

This was the most marked case of polyuria following any malarial fever which I have ever seen.

Color.—As in all febrile diseases, the color of the urine is increased, being usually reddish. It is often turbid, and deposits urates or phosphates upon standing. The color of the urine in the polyuria of convalescents is usually a pale lemon-yellow.

Acidity.—As a rule, the acidity is increased when the urine is diminished in amount, and is about normal when it is secreted freely.

Specific Gravity.—During the attack the specific gravity is increased; but, on the whole, there is little variation from normal in the specific gravity. The specific gravity of the urine in polyuria is low, being from 1.005 to 1.010.

Total Solids.—The total solids are increased, especially during the paroxysm.

Urea.—The amount of nitrogen excreted in the twenty-four hours is increased, the increase of the urea and nitrogen being most marked during the paroxysm. Sometimes this increase is noted before the fever, but, in the vast majority of cases, only directly afterwards. During the apyrexial periods the amount of urea is normal or decreased.

The urine in cases of malarial polyuria following estivo-autumnal fever generally shows a decreased amount of urea.

Uric Acid.—Rem-Pici claims that no special law controls the excretion of uric acid during the febrile attack. The amount is, however, as a rule, slightly increased in the estivo-autumnal fevers.

Chlorides.—The chlorides are not appreciably increased as a whole; but, during the first part of the estivo-autumnal attacks, they are increased during the intermissions of the fever, falling

during the febrile stage. In the polyuria following the estivo-autumnal fevers the increase in phosphates is marked.

Sodium and Potassium.—Rem-Pici found that in the estivo-autumnal malarial fevers, one-half of his cases showed diminished sodium and potassium during pyrexia, while the other half showed the diminution during apyrexia; more sodium was eliminated during the pyrexia in one-half, while in the other half more sodium was eliminated during apyrexia.

Iron.—Colasanti and Jacoangeli have demonstrated that more iron is present in the urine of malarial patients than that of other fevers, and is greater after than during the attack. It is greatest in the most severe infections.

Albumen.—In the majority of severe estivo-autumnal fevers albumen is present in greater or less amount in the urine, and is usually associated with hyaline or granular casts. All fatal cases of pernicious estivo-autumnal fever show albuminous urine prior to death. This subject will be further discussed in the chapter upon complications.

Indican.—From personal observation I believe that the amount of indican is almost invariably increased in the urine of patients suffering from the estivo-autumnal fevers.

ETIOLOGY OF THE FEVER.—In the regularly intermittent malarial fevers it is well known that the onset of the fevers is coincident with the segmentation of a group of parasites. The same is true in the estivo-autumnal fevers, although the segmentation of the parasites is not so easily observed, especially in the peripheral blood. Blood from the spleen, however, will also show a preponderance of segmenting forms, at the onset of the fevers, and, as I have shown, this occurs almost as regularly in estivo-autumnal fevers as in the tertian and quartan types of malaria.

To what is the fever due? Many and various have been the theories which have from time to time held the attention of scientists regarding this question. Laveran believed that the febrile attack is due to nerve-irritation; Richard, that it is the index of the reaction of the human organism to the malarial parasites; Golgi, that the febrile paroxysm is due to the invasion of fresh red blood-corpuscles by the young parasites, while Antolisei concluded that the invasion of the red cells by the parasites had little to do with the rise of temperature, which he believed to be due to the setting free in the blood-plasma of the newly-born parasites.

To Baccelli,* however, we owe the most reasonable theory of the rise of temperature in malaria, and the one which is to-day accepted by most authorities. He suggested that during segmentation and the entrance of the young parasites into the blood, certain toxic products were liberated, which produced the fever. These toxic products he considered to be chemical poisons of unknown nature, formed during the development of the parasites within the red blood-corpuscles and liberated during sporulation. This theory has been accepted by Marchiafava, Bignami, Mannaberg, Golgi, Thayer, and others. I believe that this theory explains most fully the rise of temperature in malarial fevers, and, reasoning from analogy, that it is without doubt correct. From our knowledge of other infectious diseases, it is impossible to believe otherwise than that the fever of malaria is due to the liberation of toxic products in the blood during the segmentation of the parasites.

While we must admit that there is no absolute proof that this is so, yet there have been certain facts ascertained which go far toward establishing the theory upon experimental evidence. Queirolo has found that the perspiration from patients suffering from malarial fever, and collected during the paroxysm, was very toxic to guinea pigs, while the perspiration from normal individuals was not. This would tend to prove that there were toxic substances liberated.

The researches of Flexner† have furnished almost conclusive proof of the truth of Baccelli's theory. He has described necrotic areas in the organs of malarial patients, focal in character, and similar to those described by other authorities in diphtheria, typhoid fever, measles, scarlet fever, etc., and which are, without doubt, due to toxic substances circulating in the blood.

In the light of our present knowledge it is probable that the *rise of temperature in all malarial fevers is due to toxic substances liberated by the parasites during sporulation.* The toxic matters found by the breaking down of the red blood-corpuscles has, I believe, but little to do with the rise of temperature.

The periodicity of the rise in temperature is easily explained by the periods of time elapsing between the sporulation of the parasites, and in the cases of continued fever, by the fact that multiple groups of parasites are present which

*"Deutsch. med. Woch.," Aug. 11, 1896

† "Journal of Experimental Medicine

intervals, thus causing an almost constant discharge of toxic matter into the circulation.

The question arises: How can the cases of sometimes pernicious malarial fever which occur without a rise of temperature be explained? Such cases undoubtedly occur, and I have myself observed a fatal case in which the temperature throughout the disease was normal or subnormal, yet in which the blood from the spleen showed numbers of sporulating estivo-autumnal parasites. As in other diseases, so in malarial fevers, many exceptions are noted to the general rule, and idiosyncrasies occur which cannot be explained. In such cases there is probably present some organismal peculiarity which prevents a rise of temperature, which we, as yet, know nothing of.

After an estivo-autumnal fever has persisted for some time, it will sometimes be noted that the fever disappears entirely or becomes modified, even though the parasites are still undergoing sporulation. While we cannot absolutely state the reason for such disappearance of the fever, it is probable that the continued action of the toxic substances upon the organism has resulted in its acquiring a relative immunity to the fever-producing toxin, or, perhaps, has stimulated the production of antitoxic substances.

CHAPTER XI

SPECIAL PATHOLOGY OF THE ESTIVO-AUTUMNAL FEVERS—ACUTE INFECTIONS

THE pathological changes occurring in the viscera are similar in infections with both the quotidian and tertian estivo-autumnal parasites, and in describing them I shall not undertake to differentiate between them.

Among those who have contributed very valuable studies upon the special pathology of malaria may be mentioned Bignami, Guarneri, Laveran, Councilman and Abbott, Bastianelli, Dock, Barker, Monti, and Thayer. In recent years our knowledge of the changes occurring in the organs in malarial infection has been greatly added to by such researches, and we have come to understand better the extensive pathological ravages of such infections. I cannot better introduce this portion of our subject than quote Marchiafava and Bignami's* admirable remarks concerning the pathology of malaria. They say: "The malarial infection develops in the blood; here only, and chiefly within the red corpuscles, can the parasite live. From this it follows that the parasite invades the red corpuscles, and nourishes itself at their expense, transforming the coloring matter of the corpuscles into black pigment (which, after the multiplication of the destruction of the parasite, is incorporated into the white cells) or otherwise injuring the red corpuscles. In consequence of this infection of the blood, we find, in addition to the destruction of the cells, a production of the detritus of the red corpuscles and of the parasites, the presence of pigmented white cells, and the penetration of erythrocytes containing parasites and of leucocytes containing pigment into the capillaries of all the organs. It can be understood from this primary localization of the infection how the principal changes must be found in the hematopoietic organs in addition to the blood, and how alterations are to be encountered in all the organs and in all the tissues." This brief summary furnishes the key to the pathology of malaria.

*"Malaria, Twentieth Century Practice," Vol. XIX, p. 227.

SPECIAL PATHOLOGY OF ACUTE ESTIVO-AUTUMNAL MALARIAL FEVER (PERNICIOUS MALARIAL FEVER)

APPEARANCE OF CADAVER.—The skin has a peculiar dusky brown or grayish hue, more pronounced the longer the infection has lasted. The wasting of the tissues depends upon the duration of the disease. Rigor mortis is generally only moderate in extent. Post-mortem discoloration occurs early and may be intense. Often a patient dead of pernicious malarial fever will resemble very markedly a yellow fever cadaver externally.

THE BRAIN.—In no organ are the pathological changes more exquisitely illustrated than in the brain, especially in those cases which have exhibited cerebral symptoms before death. In rare cases the brain will appear almost normal.

Externally the blood-vessels are generally congested, and the entire organ appears hyperemic. Small capillary hemorrhages are often observed and edema is often present. Where there have been no cerebral symptoms during life, the brain externally shows little hyperemia.

Upon section the cut surface is hyperemic, and small hemorrhages may be present in the substance. The lateral ventricles are dilated and filled with fluid, and the choroid plexus is markedly congested. The cortex, as a rule, is of a brownish or chocolate color, due to melanosis, and often the gray matter is more or less pigmented. Small hemorrhages are often found in the white substance and also in the cerebellum. In not a few cases of pernicious malaria the brain is anemic and no melanosis is present.

Microscopical Examination.—The most advantageous method of studying the microscopical changes in the brain is to harden small pieces in alcohol and section them, staining with eosin and methylene blue or Chenzinski's solution. In making such sections, portions should be taken from both the cortex and medulla of the brain. The pathological changes present are to be seen in the capillaries and in the cells of the brain.

Appearances Observed in the Capillaries.—As a rule, the capillaries are filled with blood-corpuscles, most of which contain parasites. These parasites may be observed in various stages of development or, which is very common, all of them are in about the same stage of development. If the parasites contain much pigment, the brain appears greatly pigmented, while the reverse

is also true. The parasites may be so numerous that there are hardly any uninvaded corpuscles seen, or they may be very few in number. They are sometimes so numerous as to entirely occlude the lumen of the capillaries, thus forming thrombi. The small arteries and veins are less rich in infected corpuscles. In rare cases the entire cycle of existence of the parasite can be found illustrated in one capillary. Besides infected blood-corpuscles, the following structures may be observed in the capillaries:

- a. Free parasites.
- b. Macrophages.
- c. Free pigment.
- d. Pigmented leucocytes.
- e. Endothelial cells.

a. Free parasites: In some cases large numbers of extra-cellular or free parasites, always pigmented, are observed in the capillaries. These parasites are always round, oval, or segmenting bodies, with pigment in the form of a solid, minute block, situated at or near their center. They are most numerous in cases dying of tertian estivo-autumnal fever.

b. Macrophages: Immense white blood-corpuscles containing free pigment and parasites are often seen, often so large as to distend and entirely block the capillary in which they are situated. These cells may be of endothelial origin.

c. Free pigment is present in the capillaries, and sometimes in immense quantities, blocking up the capillaries and forming thrombi. This condition is generally present in cases which have presented marked comatose symptoms.

d. Pigmented leucocytes: Most of the leucocytes present in the capillaries are pigmented, and often contain parasites enclosed in red corpuscles. The leucocytes are usually few in number.

e. Endothelial cells: The endothelial cells lining the capillaries are generally swollen and undergoing fatty degeneration; they are also pigmented and, by reason of their distension, often occlude the lumen of the capillary. They may occur free in the capillaries, and often contain parasites.

Changes in the Nerve-cells.—To Marchiafava and Monti we are indebted for valuable contributions upon the changes taking place in the nerve-cells as the result of estivo-autumnal malaria. These changes occur in both the protoplasm and the nucleus of the nerve-cell. In the protoplasm the chromatic bodies of Nissl

have disappeared, and the protoplasm appears very granular, or, in the more grave cases, the protoplasm seems to be disintegrated and rarefied.

The nucleus in such cells may appear normal, or the following changes may be noted, most often in the pyramidal cells: The nuclear membrane and nucleolus have disappeared as well as the chromatin, or one or the other of these elements may persist.

Notable changes are observed in the branches of the cortical cells, consisting of attenuation and nodal formations along them, or they present a beaded appearance. Sometimes very large, bleb-like swellings occur in their dendrites, connected by very slender filaments of protoplasm.

In rare cases nodes are observed along the axis cylinders. All the changes above described are most marked in cases of comatose pernicious estivo-autumnal fever.

The changes in the pia-mater and the spinal cord are the same as those described for the brain.

CHANGES IN THE RETINA.—Guarnieri has studied the changes occurring in the retina in pernicious malaria and finds that they consist in hemorrhages and congestion of the blood-vessels with parasite-infected red corpuscles, macrophages, pigmented leucocytes and free pigment, thus leading to impairment of function.

CHANGES IN THE LUNGS.—The gross pathology of the lungs in cases dying of pernicious estivo-autumnal fever is not characteristic, there being usually, according to the stage of the disease, hypostatic congestion, edema, broncho-pneumonia, or areas of hemorrhage present.

Microscopical Examination.—Sections from the lungs show the following changes: The alveolar capillaries are congested and often contain large numbers of pigmented, parasite-laden, white corpuscles (phagocytes) which are often much degenerated. They are most numerous in the arterioles and capillaries. The polymorphonuclear leucocytes are rarely observed. The endothelium of the capillaries is often swollen and contains small particles of pigment; but this condition is very much less marked than in the brain, liver, and spleen.

When broncho-pneumonia has occurred, the exudation into the alveoli is mostly composed of polymorphonuclear leucocytes and the alveolar cells, while only in rare instances are pigmented leucocytes or phagocytes observed, though the alveolar

capillaries are often crowded with them. Neither is free pigment common in this exudation. Marchiafava and Bignami claim that this lack of diapedesis of the pigmented leucocytes and macrophages is due to the fact that they are degenerated, and have lost the power of amoeboid motion, by which they are enabled to pass through the capillary wall.

When pneumonia complicates the estivo-autumnal fevers it is, without doubt, due to a double infection by the diplococcus of pneumonia and the estivo-autumnal parasite.

CHANGES IN THE HEART.—There is nothing characteristic in the changes occurring in the heart. The chambers of the heart, especially the right auricle, may contain clots composed of infected red blood-corpuscles and fibrin, with pigmented leucocytes and endothelial elements.

CHANGES IN THE STOMACH AND INTESTINES.—Macroscopically the only change usually observed is more or less pigmentation, the mucous membrane being of a dull slate color. In cases dying of the choleraic form of the disease, the changes are more marked, consisting of hyperemia, necrosis, and even ulceration of the mucous membrane. Peyer's patches, as well as the solitary glands, are often greatly swollen.

Microscopical Examination.—Sections of the stomach and the intestines show that the capillaries of the villi, especially, are crowded with parasite-infected corpuscles (the parasites in various stages of development or all in approximately the same stage), free parasites and pigment, phagocytes and endothelial elements. These may occlude the capillaries, forming thrombi, with resulting necrosis and ulceration of the mucous membrane in places. The epithelium lining the mucous membrane is often necrotic, and there may be present a very general superficial necrosis of the superficial layer of the mucous membrane. All the changes are most marked in choleraic pernicious estivo-autumnal malarial fever.

CHANGES IN THE LIVER.—Macroscopically the following appearances are noted: The organ is generally enlarged, often markedly so, and is of a dark slate color externally, if the disease has persisted for some time. I have seen cases in which the liver appeared almost black in color. The capsule is smooth and the liver-substance beneath appears homogeneous. Upon section, the cut surface is of a very dark brownish red or a slate color, sometimes almost black, and is bathed in blood, as the organ is gen-



erally greatly congested. It is not uncommon to find the surface mottled with yellowish spots due to fatty degeneration. The consistence of the organ is decreased, as a rule.

Microscopical Examination.—The changes noted are found in the capillaries and in the liver-cells. The capillaries contain many large macrophagi, containing much pigment and sometimes red blood-corpuscles. The number of parasites present is very limited. In the liver occur many macrophagi which seem to occlude the lumen of the capillaries in which they lie. The endothelial cells of the organ are greatly swollen and contain much free pigment and degenerated parasites. Free pigment sometimes occurs in large clumps within the liver-capillaries. The stellate cells of Kupfer are often pigmented. The changes in the liver-cells consist of atrophy, fatty degeneration, necrosis, pigmentation, and degeneration of the nuclei. The pigmentation present in the liver-cells is not due to the malarial pigment, but consists of golden yellow or brownish granules, refractive and often appearing spiked or crenated. These little pigment-granules are distributed throughout the protoplasm of the liver-cells, and it is undoubtedly derived from degenerated red blood-corpuscles. It occurs in other diseases than malaria and is most abundant toward the center of the liver-lobules.

One of the most interesting conditions present in the liver are the areas of focal necrosis which are sometimes observed. These areas are characterized by accumulations of necrotic liver-cells, leucocytes, and proliferating connective tissue-cells, and are believed by Flexner to be due to a general intoxication.

CHANGES IN THE SPLEEN. — Macroscopically, the following changes are noted: The organ is always enlarged, sometimes enormously so. Externally it is of a dark blue or almost black color, the capsule being smooth and stretched tightly. Upon section, the cut surface is of a chocolate, slate, or almost black color, and the consistence of the organ is very greatly decreased, it often being diffuent. The elements of the parenchyma can seldom be recognized.

Microscopical Examination.—As a rule, the pulp is greatly congested by multitudes of red blood-corpuscles, most of them containing parasites. I have, however, seen cases in which but few red blood-corpuscles were demonstrable in the spleen.

The cells of the splenic pulp are pushed apart by the multitudes of red corpuscles, which contain parasites in various stages

of development, the pigmented forms and the segmenting bodies being most commonly observed. Free parasites are less common but by no means rare. In cases where the disease has lasted for some days, the crescent forms are found, but never in very large numbers.

Besides the parasite-infected red corpuscles, the sections of the spleen show an immense number of phagocytes, consisting of small cells, resembling lymphocytes, and very large, often immense cells, known as macrophages. These large cells are usually filled with clumps, granules, or blocks of pigment, red corpuscles containing parasites, free parasites and segmenting bodies, degenerated red blood-corpuscles, and the smaller phagocytic cells first spoken of. The macrophages often present evidences of degeneration, as shown by necrosis of the protoplasm.

The capillaries of the spleen are crowded with infected corpuscles, while the veins contain many phagocytes. The cells of the Malpighian bodies do not become pigmented, but the fibrous trabeculae are greatly pigmented. Free pigment is present throughout the pulp sinuses, lying in large blocks or clumps, or in the form of small rods and granules.

Here, as in the liver, two forms of pigment occur: the dark brown, or nearly black, malarial pigment, and the golden yellow pigment derived from the degenerated and broken down red blood-corpuscles.

CHANGES IN THE KIDNEYS.—As a rule, the macroscopical appearance of the kidneys is normal, but sometimes acute congestion and pigmentation are present. An acute parenchymatous nephritis is by no means rare, accompanied by small hemorrhages in the cortex of the organ.

Microscopical Examination.—The changes observed microscopically in the kidneys are much less marked than in the other viscera, especially the brain, liver, and spleen.

The Malpighian tufts are often found congested and the seat of small capillary hemorrhages. There is but little pigmentation generally, but sometimes the glomeruli appear much pigmented. The pigment is situated within the leucocytes, the capillaries, and in the endothelial and epithelial cells. Parasites, either free or within the red corpuscles, may be seen occasionally within the glomerular capillaries, but they are few in number: The epithelium of Bowman's capsule is generally undergoing proliferation, and the capsular space may be occluded by fibrinous material.

The epithelium lining the convoluted tubules is undergoing degenerative changes, fatty degeneration, and necrosis. The straight tubules often contain hyalin, epithelial, or granular casts. The intertubular capillaries are somewhat congested, and in them free pigment in small amount is observed, as well as endoglobular parasites, pigmented leucocytes, and large macrophages. All these, however, occur in very much smaller numbers than in the capillaries of the brain, liver, or spleen.

CHANGES IN THE BONE-MARROW.—Macroscopically the bone-marrow varies in color according to the length of time the infection has existed. In the long bones, in recent cases, the normal yellow color of the bone-marrow is found; while if the infection has lasted for some time, as weeks or months, the color varies from red to dull black. In acute cases the bone-marrow is very soft, even diffuent.

Microscopical Examination.—In sections of bone-marrow the following appearances are noted: The capillary vessels contain numerous endocorpuseular parasites, in advanced stages of development, sporulating bodies, and, if the infection has persisted long enough, crescentic organisms. They also contain numerous macrophages, containing granules and clumps of pigment, as well as red blood-corpuscles. Numerous free segments are generally found in the smaller vessels. Externally to the vessels, in the marrow pulp, parasites are found in various stages of development, including crescents. Here are also found large numbers of macrophages, many of which are undergoing degenerative changes. Nucleated red corpuscles are common, as well as pigmented medullary cells.

The changes found in the other viscera possess but little pathological importance.

I insert here the autopsy record of a case of pernicious quotidian estivo-autumnal malarial fever, which well illustrates the pathological findings in these fevers. This case had had several attacks of the fever before the one which proved fatal:

AUTOPSY UPON THE BODY OF R. G. CRAWFORD, TEAMSTER

Died 4:30 a. m., July 21, 1900. Age, 52 years. Clinical Diagnosis: Pernicious Quotidian Estivo-autumnal Fever.

Body that of a man apparently 50 years of age, somewhat emaciated. Skin yellowish. Rigor mortis slight. Post-mortem

discoloration over dependent portions of body. Finger-nails not congested. Pupils irregularly dilated.

Brain.—Dura mater appears normal. The amount of cerebrospinal fluid is increased. The surface of the cerebrum is pale, and upon section the medullary appears hyperemic and the cortex is slate-colored. The lateral ventricles are filled with fluid. The choroid plexus is not congested. Upon section, the cut surface of the cerebellum appears normal, save for congestion. Externally, the blood-vessels of the cerebrum are congested.

Thoracic and Abdominal Cavities.—The subcutaneous fat and muscular tissue is normal in amount. The pleural cavities are free from fluid. The liver reaches about one centimeter below the border of the last rib. The omentum contains a large amount of fat, and reaches to a level with the umbilicus. The appendix is about three centimeters in length, and lies in the right iliac fossa; it is normal in appearance. The bladder is dilated. The abdominal aorta shows no evidence of sclerosis. The suprarenal glands appear normal.

Liver.—The liver measures 28 x 21 centimeters. It is dark in color externally. The gall bladder contains a large number of gall-stones and inspissated bile. Upon section, the cut surface of the liver is slate-colored and the lobules are ill-defined. The organ is congested. Weight, 1,640 grams.

Spleen.—The spleen measures 19 x 12 centimeters. The organ is purplish black in color externally. The capsule is smooth. Upon section, the cut surface appears almost black in color, with light areas scattered throughout. The consistence of the organ is very much diminished, it being almost diffuent. Weight, 440 grams.

Pancreas.—The pancreas measures 22 x 4½ centimeters. Upon section, the cut surface appears congested. Weight, 115 grams.

Left Kidney.—The organ is pale in color. The capsule is smooth and slightly adherent. Upon section, the cut surface is congested. The cortex and pyramids are distinct, and the cortex is above normal in thickness. Weight, 125 grams.

Right Kidney.—The organ is somewhat lobulated. The capsule is slightly adherent; otherwise it resembles the left. Weight, 125 grams.

Lungs.—The lungs are crepitant throughout and appear normal.

The Pericardial Cavity contains about three centimeters of clear straw-colored fluid.

Heart.—The amount of extra-cardial fat is increased. The vessels are congested. Upon section, the ventricles contain small clots. The muscular walls are about normal in thickness. The valves of the heart are normal, with the exception of the middle segment of the pulmonary valve, which contains numerous small apertures.

Intestines.—The mucous membrane is congested, otherwise they are normal.

MICROSCOPICAL EXAMINATION.—*Liver.*—Sections of the liver show the pathological lesions of cloudy swelling and the changes found in pernicious malarial fever.

The fibrous tissue in the portal spaces has slightly increased in amount, and there are large numbers of connective-tissue cells present. All the blood-vessels in the organ are increased in thickness. The liver-cells are swollen, smoky, and granular in appearance, and in many of them the nucleus has entirely disappeared. In others, the nucleus is present and shows necrotic changes, as evidenced by the pale stain and the granules of chromatin, which are widely separated or are collected in small clumps.

The protoplasm of the liver-cells contains much fine yellow pigment, which seems to be distributed only in the protoplasm and not in the nucleus.

The intralobular capillaries contain a great deal of black pigment, numerous large macrophages and smaller mononuclear leucocytes. The pigment which is free in the capillaries is in the form of irregular blocks, and none of the yellow pigment which is present in the liver-cells is seen in the capillaries. The large macrophages which crowd the capillaries contain within their protoplasm an immense amount of black pigment, evidently derived from broken-down malarial parasites; they also contain blood-corpuscles containing parasites, and free parasites of the estivo-autumnal variety. The number of parasites present is comparatively small, but the amount of pigment present is immense, and in clumps so large that many of the capillaries are occluded by it. This is especially noticeable in the capillaries near the portal spaces. On account of the small caliber of the interlobular capillaries the large macrophages are compressed, and they appear often as long, slender, pigment-bearing cells. Some of these leucocytes are so large as to entirely block the capillaries. The malarial parasites present are

small, round, or oval bodies, containing a few small granules or grains of pigment, generally collected at the center. These are presegmenting parasites. No crescent forms were observed in the liver. The stellate cells of the Kupfer contain black pigment and sometimes small parasites.

In numerous places throughout the capillaries of the liver there are large bleb-like parasites containing pigment, which are evidently degenerating. The pigment in the macrophages is in the form of small round blocks, or larger irregular collections, and is dark brown or almost black in color. There is not a single capillary in the section that does not show pigment-bearing cells.

Spleen.—Sections of the spleen show the changes characteristic of pernicious malarial fever.

The Malpighian bodies are somewhat fibrous, and at their border there is an immense amount of yellowish black pigment. The splenic pulp contains a small number of red corpuscles which contain small, round or oval, estivo-autumnal parasites, which are pigmented. There is not the usual number of red corpuscles present in this spleen that we generally find in spleens from cases of pernicious malaria. The splenic pulp also contains immense numbers of pigment cells, or macrophages, and large masses of free pigment. The macrophages are large white cells, which contain the following objects: (1) large, irregular collections of brownish black pigment; (2) red corpuscles containing small, round, pigmented, estivo-autumnal parasites; (3) free estivo-autumnal parasites, most of them pigmented and showing signs of segmenting; (4) fine granules of a yellowish pigment which is entirely distinct from the black pigment present.

Some of the macrophages show all of these within their protoplasm, while others, and they in the majority, show only one or two free parasites and irregular collections of pigment. As a rule, these white cells are about six times the size of a blood-corpuscle, but some of them are present which are very much larger. These very large cells entirely block the capillaries of the organ, thus hindering the circulation.

Besides the macrophages, there are numerous mononuclear leucocytes and endothelial cells which do not take up the pigment of the parasites. The polymorphonuclear leucocytes are comparatively few in number. Everywhere throughout the section there are very large masses of free pigment situated in the

spaces of the splenic pulp, often so large as to rupture them and cause an area of necrosis in which they are situated.

Throughout the spleen may be seen crescentic forms of the quotidian estivo-autumnal parasite, but they are comparatively few in number. These crescents appear exactly as they do in the peripheral blood. In the spleen there are also numerous large bleb-like parasites, like those seen in the liver, which contain much pigment and numerous vacuoles. These are evidently degenerating bodies. The segmenting forms of the parasite are remarkably few in number in the sections of the spleen, but many of the macrophages contain segmenting bodies.

Kidney.—Sections of the kidney show the pathological lesions of acute nephritis and the changes present in pernicious malaria. The Malpighian bodies are greatly congested, the capillaries being filled with blood and some of them have ruptured, thus causing hemorrhages within the tufts. Many of these capillaries contain small, free, round or oval parasites, containing a small clump of pigment at their center. The capillaries also contain a few red cells which are infected by the parasites. There is present a small amount of free pigment.

In the capillaries may be seen, now and then, a large bleb-like body, evidently a degenerated parasite, like those seen in the liver and spleen.

The number of infected corpuscles and free parasites, and the amount of pigment, is very much smaller than in the case of the liver and spleen. No crescent forms were observed in the Malpighian bodies.

The epithelium of the tubules is much swollen and is rapidly proliferating, while the protoplasm of the cells is smoky and finely granular in appearance and contains, in many instances, pigment-grains of a yellowish color.

One of the most interesting features of the kidney-sections is the occurrence, within many of the tubules, of collections of black pigment and here and there a few parasites. There are few parasite-infected red blood-corpuscles present in the tubules. The capillaries between the tubules contain numerous free parasites, round or oval in shape, and pigmented, also macrophages and infected red corpuscles. The macrophages, as in the liver and spleen, contain free pigment and parasites, red corpuscles containing parasites or yellowish pigment. The walls of the capillaries are not thickened. It is especially noticeable how

slight the amount of pigment is in the kidney as compared with the liver and spleen, and how few parasites are present.

Brain.—Sections of the brain show the pathological lesions of pernicious estivo-autumnal fever of comatose type. The changes observed in the sections of the brain may be divided into those occurring within the capillaries and those within the brain substance proper. The small capillaries of the brain, especially those of the cortex, are crowded with pigmented, free parasites, leucocytes containing pigment, and in some places by small collections of yellow pigment. The infected capillaries are most numerous in the cortical portion of the brain, but they are by no means rare in the medullary portion. The pigment within the capillaries is generally collected in irregular masses, is brownish-black in color, and, in some places, entirely occludes the lumen of the capillary. This condition, which is very noticeable throughout the sections, no doubt accounts for the symptoms present, referable to the brain.

The parasites present in the capillaries are mostly free, are oval or circular in shape, small, and contain pigment which is generally collected near the center, in the form of a small grain or collection of grains. It is remarkable how uniform these parasites are in appearance and how rarely is seen a red cell infected by parasites. It may be that during the preparation of the specimen the red cells became disintegrated; but this is hardly probable. In some places the capillaries are occluded by large white cells (macrophages) containing much pigment and numerous free parasites. Taken as a whole, the amount of pigment present in the brain is not large.

The changes occurring within the substance of the brain consist in a necrosis of the protoplasm of some of the cells, as is evidenced by the irregular staining of the protoplasm and nuclei.

Sections were not made of the stomach and intestines, as they presented no evidences of malarial infection.

CHAPTER XII

CLINICAL DESCRIPTION OF THE ESTIVO-AUTUMNAL FEVERS— CLASSIFICATION AND SYMPTOMATOLOGY OF THE TERTIAN AND QUOTIDIAN FORMS—ANALYSIS OF SYMPTOMS AND PHYSI- CAL EXAMINATION—EXAMINATION OF THE BLOOD

CLASSIFICATION.—As stated in the opening chapters of this work, I hold with Marchiafava and Bignami that there are two distinct types of estivo-autumnal malarial fever, both from a clinical and etiological standpoint.

Clinically, all estivo-autumnal fevers should be classed as *severe* forms of malarial fever, in contradistinction to the tertian and quartan infections, which are classed as *mild* forms of malarial fever. This classification of the estivo-autumnal infections as severe forms is most important. While, of course, every case of such infection does not result fatally, and while most are readily amenable to treatment and many are cured spontaneously, still the fact remains that almost all the pernicious malarial fevers are caused by the estivo-autumnal parasites, and every case showing the presence in the blood of such parasites should be considered as serious in nature.

The idea that there is a parasite peculiar to the pernicious malarial fevers, which is alone capable of producing them, is one which has been long ago exploded and is entirely false. The estivo-autumnal parasites occurring in the blood of such cases differ in no way from those occurring in estivo-autumnal fever in general, hence the danger that any infection due to these parasites may become pernicious or malignant in character.

As is well known, the estivo-autumnal fevers occur most frequently, in temperate climates, in the summer and autumn, especially during the months of July, August, September and October; but in the tropics, and indeed in subtropical countries, this type of infection is present throughout the year and supplies the greater part of the malarial fevers of these regions. From this it will be seen that the time of the occurrence of these fevers is purely a geographical proposition. In the United States, for in-

stance, such fevers occur in the summer and autumn, as a rule, while in the Philippine Islands they are present throughout the year. Relapses of estivo-autumnal fever may, however, occur at any time, and a careful distinction should be made, in temperate climates, between such relapses and primary attacks.

It should be distinctly understood that either the tertian or quotidian estivo-autumnal parasite is capable of producing pernicious symptoms. As to which is most often associated with pernicious malarial fever, I am as yet, from personal observations, unable to say. Marchiafava and Bignami have found that in the malarial fevers of Italy the tertian estivo-autumnal parasite is most often found, whereas I have most often found the quotidian parasite in cases infected in Cuba and the Philippines. I believe that, in all probability, one occurs about as frequently as the other, and that it is premature to consider either as peculiar to malignant infections. It is probably the susceptibility of the patient and the number of parasites present which determines the pernicious character of the fever rather than the variety of the estivo-autumnal parasite present.

In previous chapters I have considered the morphological differences between the tertian and quotidian parasites, but we do not have to rely only upon such facts, for both varieties of the fever are distinct clinically, in uncomplicated cases. I am aware that many American observers have failed to distinguish the two types of fever which are here described, but I am convinced that it has been because of insufficient study of the cases without quinine, and also because the most typical cases occur in the tropics.

I feel sure that an unprejudiced observer will admit that Marchiafava and Bignami's classification is correct, both from an etiological and clinical point of view, if he studies uncomplicated cases of estivo-autumnal malarial fever in which quinine has not been recently given. Certainly nothing could be more distinct, clinically, than typical cases of tertian and quotidian estivo-autumnal malarial fever.

As to the frequency of the occurrence of the two types of fever, it is undoubtedly true that the tertian form is altogether the most common. From the data which I possess, comprising several hundred cases of estivo-autumnal fever, the tertian parasite was present in about 75 per cent of the cases.

Before considering the symptomatology of these fevers, the

impression which prevails among certain physicians, that a remittent temperature is characteristic of them, deserves a short consideration. In the first place, this impression is a false one. Irregularity or remittance is not at all characteristic of the estivo-autumnal fevers. These fevers, if uncomplicated, are just as regular in their manifestations as either the simple tertian or quartan fevers, in the great majority of cases. I am willing to admit that irregularities of temperature are more apt to occur in estivo-autumnal cases than in tertian or quartan cases, but that such irregularities are characteristic of them, I am satisfied is untrue. Any malarial fever may become irregular, such irregularity being due to a multitude of causes, one of the chief of which is the unscientific use of quinine.

From a consideration of the temperature curves the estivo-autumnal fevers may be divided, clinically, as follows: Tertian, quotidian, irregular, and remittent or continued.

Some authorities have striven to establish a class of malarial fevers characterized by long intervals between the paroxysms, in which six, eight, or even ten days elapse between the attacks of fever. Such a classification is a remnant of the "Dark Ages of Medicine" and is undeserving of consideration. Such cases are simply relapses of a previous malarial infection and are as apt to be due to the tertian or quartan parasites as to the estivo-autumnal. Now and then a case is observed which apparently shows some such irregularity, but it is only apparent, for an examination of the blood will demonstrate that the cycle of existence of the particular parasite causing it is completed, as usual, although the clinical symptoms may be atypical; in other words, the infection is *latent*.

SYMPTOMATOLOGY OF THE ESTIVO-AUTUMNAL MALARIAL FEVERS

In considering this portion of our subject, I shall divide it, from a clinical point of view, as follows:

1. The Tertian Estivo-autumnal Fever.
2. The Quotidian Estivo-autumnal Fever.
3. Pernicious Estivo-autumnal Fever.
4. Latent or Masked Estivo-autumnal Fever.

TERTIAN ESTIVO-AUTUMNAL FEVER.—A patient suffering from this form of estivo-autumnal fever presents, as a rule, the following symptoms:

Prodromal.—The prodromal symptoms are loss of appetite, slight headache, more or less dull pain in the back and legs, frequent urination, nervousness, and a general feeling of "unwellness" and malaise.

Symptoms During the Paroxysm.—As a rule three stages may be distinguished in the paroxysm.

The Cold Stage.—This is generally initiated by yawning and a feeling of weakness and slight headache. In the majority of cases there is no distinct chill, but chilly sensations are most often noticed along the spinal column, consisting of evanescent "creeping" sensations.

At the same time, marked malaise develops, sometimes very extreme, together with nausea and vomiting in some cases; the headache increases and the patient is mentally depressed. The skin presents the well-known appearance of "goose flesh," and it and the mucous membranes are cyanosed; the extremities are cold and feel heavy to the patient. The legs and back ache, the pain being greatest in the lumbar region; the tongue is broad and flabby, and heavily coated; the respirations rapid, and the pulse is weak, rapid, and often irregular. As a rule, the cold stage does not last more than half an hour, and the patient seldom shakes with the chill, as in the simple tertian. The temperature is elevated.

The Hot Stage.—Gradually the patient experiences a sensation of heat, coming first as localized flushings, but soon becoming general. The eyes are suffused and brilliant, the face red, the entire skin dry and hot. The pulse is rapid and dicrotic, the respiration hurried and apparently somewhat difficult; the headache is intense, and there is either great mental depression or nervous excitement; the pain in the back and limbs increases and is often almost agonizing. The temperature is elevated, and the curve is very characteristic; the nausea continues and vomiting may occur repeatedly; diarrhoea may occur, and polyuria is not uncommon. This stage lasts for several hours and is succeeded by the

Stage of Remission.—During this stage the symptoms become milder and gradually disappear; the temperature becomes normal or subnormal, and slight sweating occurs, as a rule. Headache often remains during the intermission.

As a rule, attacks of tertian estivo-autumnal malaria occur toward evening, extend throughout the next day, and subside

during the first hours of the third day, the paroxysm thus lasting thirty-six hours or more, and recurring every forty-eight hours.

QUOTIDIAN ESTIVO-AUTUMNAL FEVER.—*Prodromal Symptoms.*—The prodromal symptoms are the same as those observed in the tertian form of the fever.

Symptoms During the Paroxysm.—As in the tertian form, the three stages described may generally be observed, but in this form a distinct chill is much more commonly observed, the patient often shaking with it. The other symptoms are essentially the same, save that the temperature curve is not so characteristic. The attacks most often occur toward evening and recur every twenty-four hours.

ANALYSIS OF THE SYMPTOMS OF THE TERTIAN AND QUOTIDIAN FORMS OF ESTIVO-AUTUMNAL MALARIAL FEVER

Temperature Curve in Tertian Estivo-Autumnal Fever.—In uncomplicated cases of tertian estivo-autumnal fever, in which no quinine has been given for the first three days, the temperature curve is absolutely typical and a diagnosis could be arrived at from it alone, for in no other disease is such a temperature exhibited. The onset of the fever is abrupt, there being a sudden rise of temperature to 103° or 104° F. as a rule; following this there occur slight oscillations in the temperature, covering several hours, in which the temperature falls from one-half to one degree; this period of oscillation in the temperature curve is followed by a distinct fall or pseudo-crisis, in which the temperature drops from one and one-half to two, or even three, degrees. This fall in the temperature is often so extreme that one receives the impression that it is the real crisis; on the contrary, however, the fever again rises to a higher point than it had before attained, and then follows the true crisis, in which the temperature falls generally below normal. From this it will be seen that the temperature curve may be divided into five stages: 1, the initial rise; 2, the period of slight remissions or oscillations; 3, the pseudo-crisis; 4, the precritical rise; 5, the true crisis. This typical temperature curve is well illustrated in Chart No. 1.

As will be seen, the fever lasts for many hours, generally over twenty-four, and often from thirty-eight to forty. That is to say, the paroxysms really cover two days, but as the initial

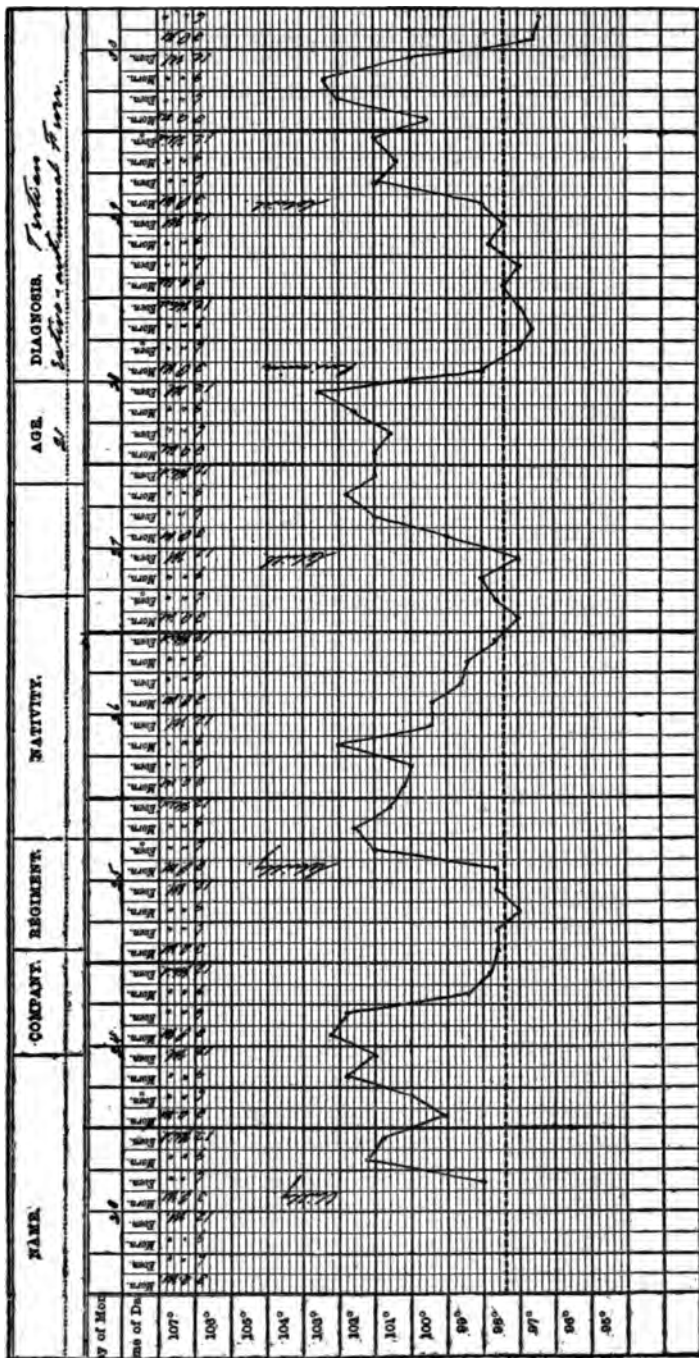


Chart No. 1. Typical Temperature Curve of Tertian Estivo-autumnal Malarial Fever.

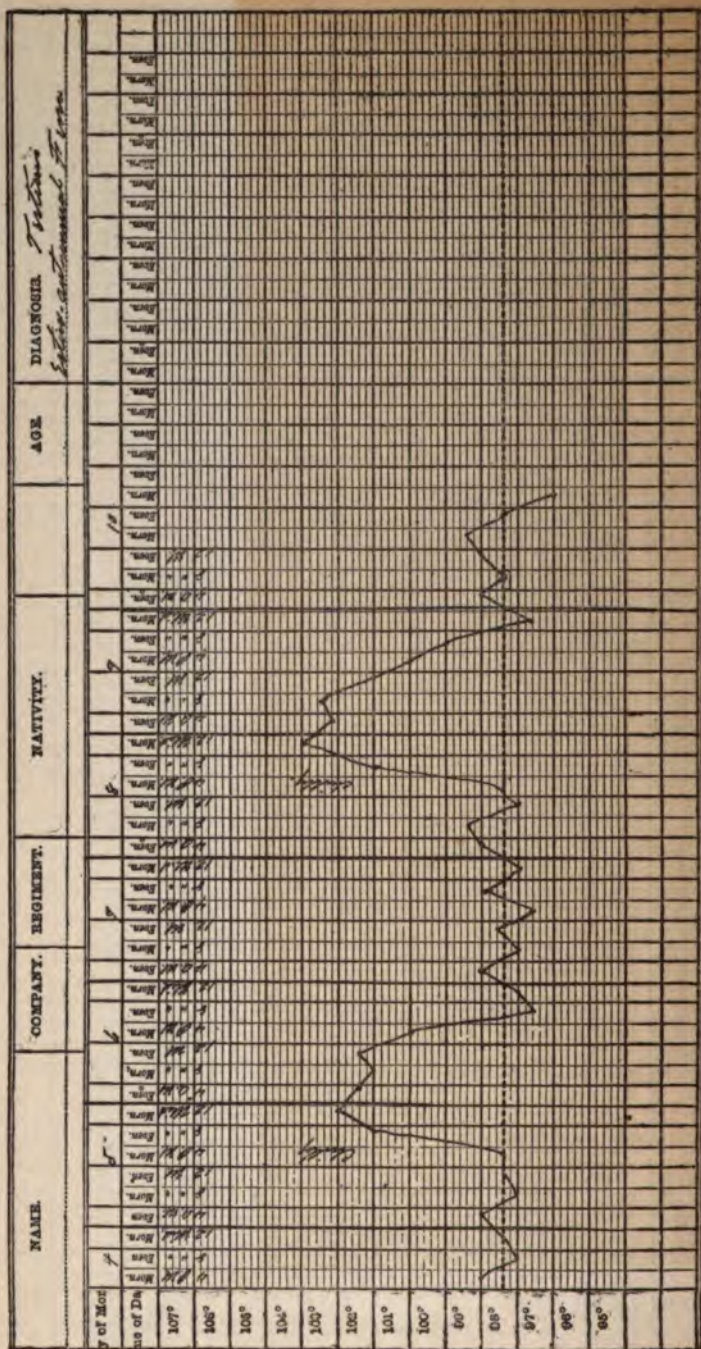


Chart No. 2. Tertian Estivo-autumnal Malarial Fever, showing short duration of the paroxysm.

rise occurs every third day, the fever is essentially tertian in character. It differs markedly from the simple tertian as regards the temperature curve, that of the simple tertian only resembling it when a double tertian infection occurs in which the two groups of parasites mature within a few hours of one another, thus causing a more or less continuous fever. In the estivo-autumnal tertian there is no day in which fever is absent; whereas in the simple tertian, the day intervening between the paroxysms is free from fever.

In a large proportion of cases of tertian estivo-autumnal fever, the characteristic temperature curve described will be exhibited; but there are many deviations from the classical type. These deviations are due to several factors, among the most important of which are the following: improper medication with quinine; double infections or infections with more than one variety of the malarial parasite; anticipation of the attacks, especially common in the pernicious fevers; retardation of the attacks; slight elevations of temperature between the attacks, and complication with some other disease.

The most beautifully typical tertian estivo-autumnal temperature curve may be rendered atypical and very confusing by the administration of small doses of quinine at irregular intervals; and this is one of the greatest stumbling blocks in the way of a correct clinical diagnosis of the disease.

The chief alterations in the temperature curve produced by these various factors are:

1. A curve almost identical with that of a simple tertian, produced by the short duration of the paroxysm. (Chart No. 2.)
2. A curve characterized by a long period of slight remissions, due to prolongation of the paroxysm. (Chart No. 3.)
3. A curve showing no well-marked initial elevation of temperature, thus causing a more or less continuous fever line.
4. A continuous curve showing only slight remissions, due to overlapping of the paroxysms. (Chart No. 4.)
5. A curve showing a very marked pseudo-crisis, thus causing the fever-line to resemble that of a double tertian or quotidian estivo-autumnal infection.
6. A curve in which the five stages described are reversed.

Besides these modifications there occur many which are so complex that it is impossible to recognize with what disease we are dealing without an examination of the blood by the micro-

scope. Such complex temperature curves are most often due to the administration of quinine in an improper manner.

It may be well to state here that a chart which shows only the morning and evening temperature is far worse than useless in tertian or quotidian estivo-autumnal fever, and should be carefully guarded against. The temperature should be taken at least every four hours, and to secure the most typical charts it should be taken every three hours. In these cases a morning and evening chart is inexcusable.

Temperature Curve in Quotidian Estivo-autumnal Fever.—In the quotidian form of the disease the temperature curve is not very characteristic. It consists essentially in an abrupt rise of temperature to 103° F. or above, succeeded by as abrupt a fall, the entire attack lasting, as a rule about eight hours, but sometimes longer, while in the typical form the temperature, during the crisis, generally falls below normal. This is a very marked peculiarity of the quotidian form, the temperature almost invariably falling below normal, quite often to 95° F., and some times below. (Chart No. 5.) In no other disease does the temperature fall so far below the normal without a fatal result to the patient.

The temperature curve in the quotidian form seldom remains regular for long at a time, as the attacks tend to run into one another, thus giving rise to a more or less continuous fever. This is especially true in those cases assuming a pernicious type, but not in all such cases, for I have seen fatal cases in which the temperature curve remained very regular.

As will be seen, the curve in the quotidian form of estivo-autumnal fever is not very characteristic, resembling very closely that of an ordinary double tertian infection, and we must, therefore, depend upon the microscope in making our diagnosis. There is no greater proof of the value of a microscopical examination of the blood than is found in the ease with which the various forms of malarial fever are diagnosed and differentiated by it, and such an examination is often instrumental in saving life.

The Chills.—As a rule, in the estivo-autumnal malarial fevers, in contradistinction to the tertian and quartan fevers, the chill is slight or almost absent. In the majority of cases the patients simply complain of chilly sensations along the spinal column, and seldom shake severely. This is especially true of the tertian infections. In the quotidian form the chill is generally

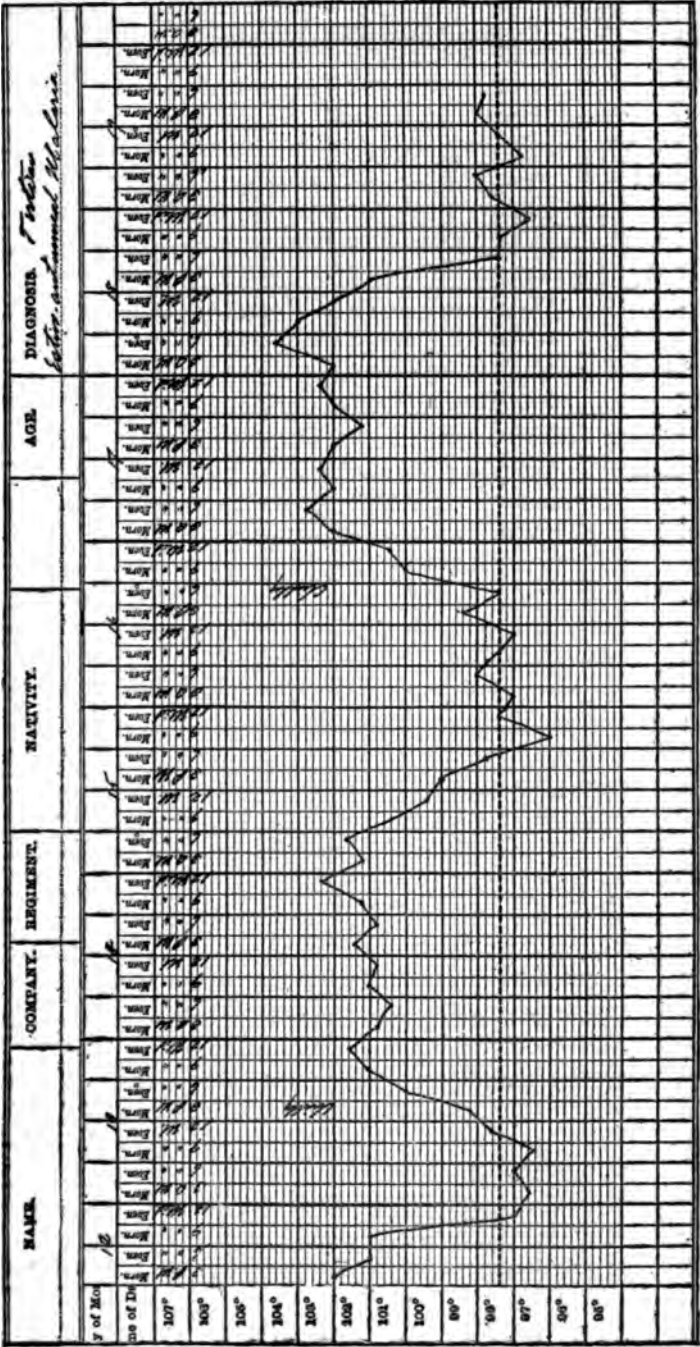


Chart No. 3. Tertian Estivo-autumnal Malarial Fever, showing long stage of slight remissions.

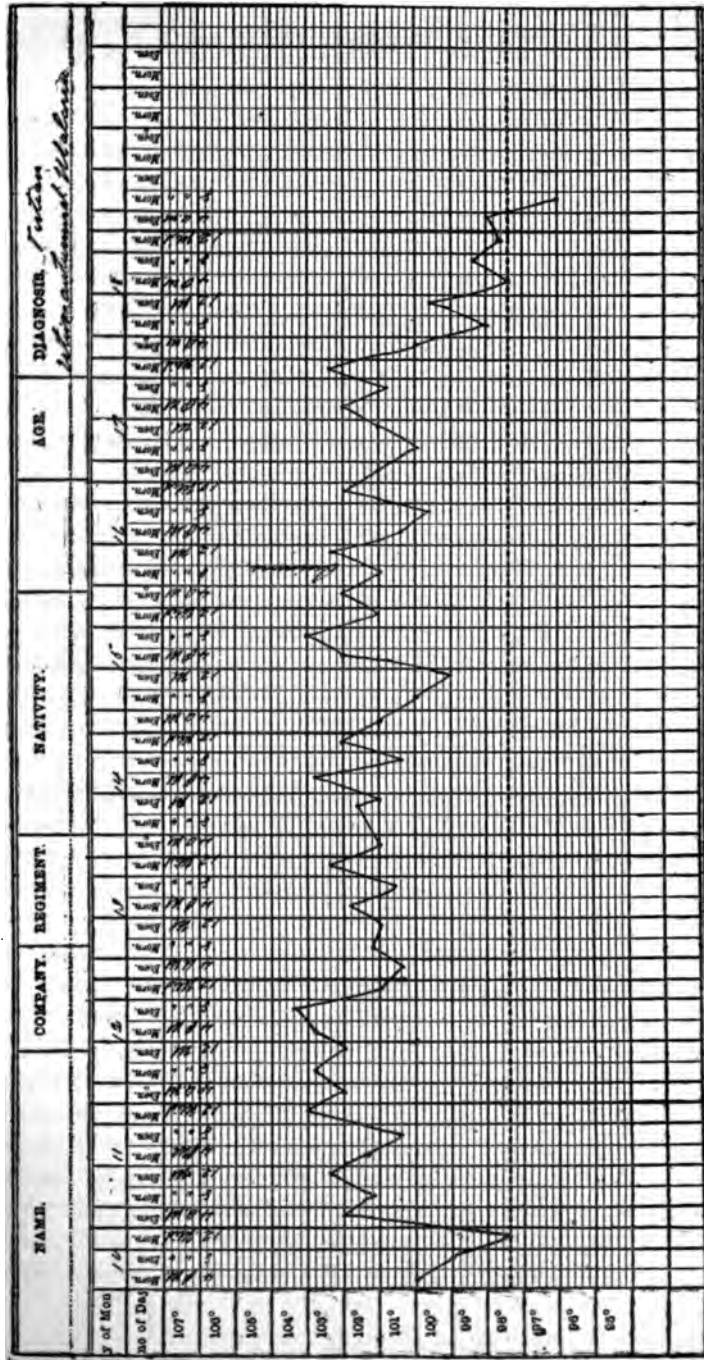


Chart No. 4. Tertian Estivo-autumnal Malarial Fever, showing continuous temperature curves.

present and more pronounced, and in both occur cases in which the chill is very severe and exhausting. There are also many cases in which the chill is absent or so slight as not to attract the attention of the patient. As a rule, the chilly sensations, or the chill, do not last over three-quarters of an hour, at the longest, and often not over ten or fifteen minutes.

The Sweating.—In the tertian estivo-autumnal fever the sweating is not excessive, and is often so slight as not to attract attention. In the quotidian form the sweating is generally more severe, but not, as a rule, so marked as in the simple tertian or quartan malarial fevers. In both forms, however, the sweating stage may be prolonged and exhausting, the amount of perspiration being excessive.

Facial Appearance.—In primary acute attacks, both of the tertian and quotidian estivo-autumnal fevers, the face is flushed or congested, the eyes brilliant, the conjunctivæ congested. An anxious expression is often present, and the patient looks very sick. Exceptions to this rule are noted in which the face is pale and the patient appears indifferent or even cheerful. In cases which have suffered from relapses the face is usually brownish yellow in color, slightly flushed and haggard-appearing.

The Skin.—In primary acute attacks of both forms of these fevers the skin usually appears normal in color, but where relapses have occurred it usually has a brownish yellow, anemic appearance. During the fever certain eruptions, or rashes, may appear upon the skin, especially *urticarial* eruptions, which I have observed very often.

Peeling of the skin is sometimes observed, occurring toward the latter part of an acute attack. I remember such a case, in which the peeling was very extensive, portions of the epidermis several centimeters in diameter separating.

One of the most frequent conditions present in both these forms of estivo-autumnal fever is herpes of the lips. This occurs in quite a large proportion of the cases. Herpes of the nose is also common. In several cases I have observed herpes of the penis occurring with or immediately after a paroxysm.

The Mouth and Tongue.—The mouth, during the paroxysms, is dry, the tongue thickly coated with a dirty white or brownish fur, and either broad and flat or pointed and narrow. In severe cases the tongue is dry and coated with a thick brown fur, and in pernicious cases sordes may form upon the teeth as in typhoid.

SYMPTOMS CONNECTED WITH THE CIRCULATORY SYSTEM.—The heart-sounds are generally clear, but often a slight systolic souffle may be heard. In many cases, however, the heart-sounds are muffled or the second sound is increased in volume.

The *pulse* is weak and rapid; it is easily compressible and remarkably dicrotic in the majority of cases. In not a few cases it will be found intermittent, and sometimes alarmingly irregular. In many cases the patient complains of a dull or acute pain over the heart, which is in all probability neuralgic in character. The area of heart-dullness is not altered in uncomplicated cases.

SYMPTOMS CONNECTED WITH THE RESPIRATORY SYSTEM.—The respirations, in an acute attack of these fevers, are always quickened and often appear to be slightly labored. This is due to the greater or lesser amount of congestion present in the lungs and the high fever. A slight cough is a very frequent symptom.

Physical examination of the lungs may show slight areas of lessened resonance and rales, chiefly sibilant in character. Moist rales are sometimes heard. A mild catarrhal *bronchitis* is of frequent occurrence.

SYMPTOMS CONNECTED WITH THE DIGESTIVE SYSTEM.—*Nausea* is a very common symptom, occurring in about 90 per cent of all cases, and is often very distressing and exhausting.

Vomiting occurs in a large proportion of the cases, and sometimes is so severe and persistent as to endanger the patient's life.

Pain over the stomach is a common symptom and may be agonizing in character. Loss of appetite and loathing of food are common symptoms during the paroxysms. Pain over the abdomen is sometimes complained of, and may be so severe as to simulate peritonitis. In rare cases it may be localized in the region of the appendix, and simulate appendicitis.

Diarrhœa is a common symptom, occurring during the paroxysm as a rule.

Constipation is not rare during the early portion of an attack.

SYMPTOMS CONNECTED WITH THE GLANDULAR SYSTEM.—Enlargement of the *spleen* is almost invariably present, the organ being plainly palpable and often extending very nearly to the umbilicus, or beyond it. In recent infections it is soft and rounded, and very tender upon pressure, while in old infections it is hard, and presents a well-defined, rather sharp margin.

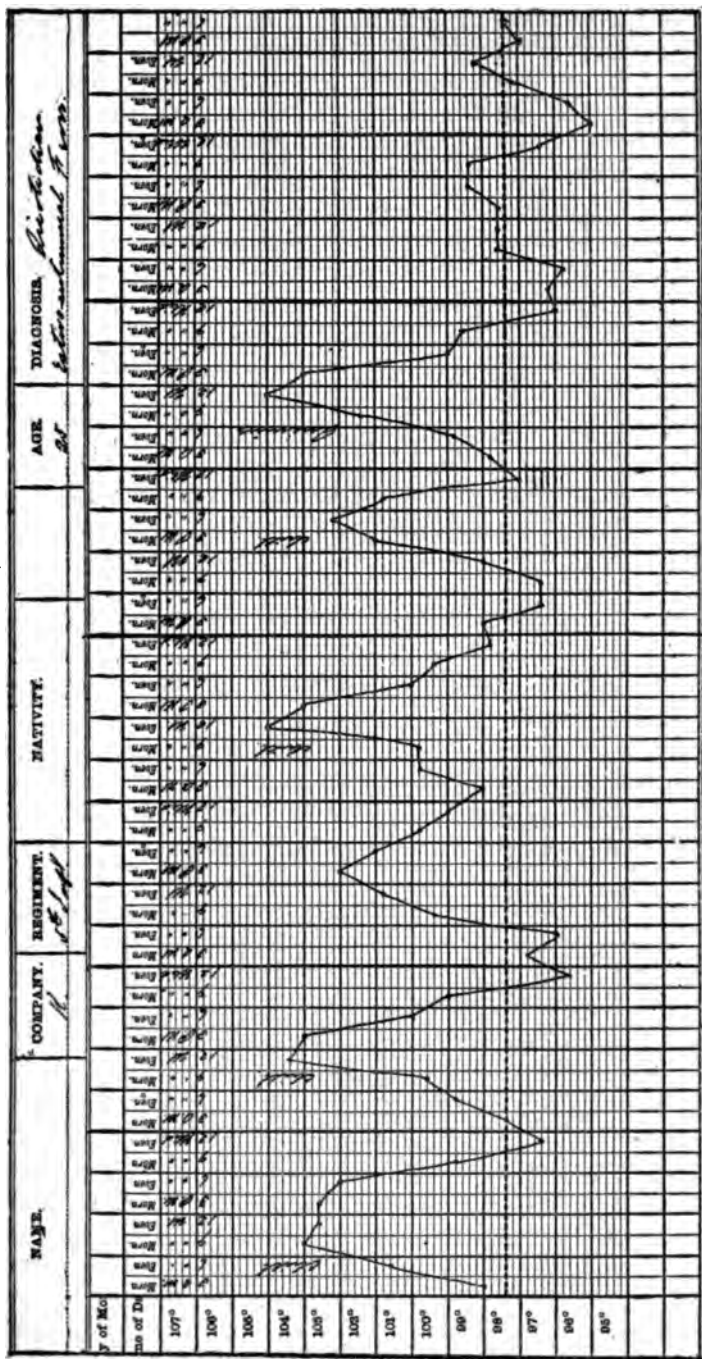


Chart No. 5. Typical Temperature Curve of Quotidian Estivo-autumnal Malarial Fever.

The *liver* is often enlarged and tender, especially in cases which have often suffered from relapses.

SYMPTOMS CONNECTED WITH THE URINARY SYSTEM.—In many cases a *polyuria* exists before, during, or after a paroxysm.

Pain over the kidneys is a very common symptom, but it is doubtful whether it is referable to these organs.

Albuminuria is rather common, and will be discussed in the chapter upon complications.

SYMPTOMS CONNECTED WITH THE NERVOUS SYSTEM.—*Delirium* occurs in a fairly large percentage of the cases, and is usually of a mild type; active maniacal delirium is sometimes observed.

Stupor is a common accompaniment of the more severe forms of estivo-autumnal fever.

Coma is common in pernicious cases and is often of very serious import.

Headache is a most common symptom. It is usually referred to the forehead and occiput, and is often almost unbearable. It persists, as a rule, throughout the paroxysm, and often in the interval.

Vertigo and *tinnitus aurium* are also common symptoms and are very annoying.

Pain in the back and limbs is always present and is generally one of the hardest things which the patient is called upon to bear. The pain is usually of a dull aching character, but may be sharp and radiating. Patients suffering from either the tertian or quotidian forms of estivo-autumnal fever are often extremely nervous, both during and between the paroxysms, and this condition not very rarely deepens into a mild form of melancholia; such cases should be carefully watched, as suicidal tendencies are apt to develop.

In closing this summary of the symptomatology of the estivo-autumnal fevers, it is but proper to say that many cases will present but a few of these symptoms, while others will present nearly all of them; no hard and fast rule can be laid down regarding the symptomatology of these forms of malaria. Many will resemble typhoid fever in their course and symptoms, and in such cases we must depend upon the microscope in making our diagnosis; others will resemble nothing "in the heavens above or in the earth beneath," and here again the microscope will be of inestimable value; there will be others so typical that "he who

runs may read," but even in these the use of the microscope should never be neglected, for the examination of the blood is always essential in making a scientific diagnosis.

EXAMINATION OF THE BLOOD DURING THE CLINICAL PERIODS OF THE DISEASE.—For convenience I have tabulated below the various phases of the tertian and quotidian estivo-autumnal parasites visible in the blood at various periods of the infection.

The Tertian Estivo-autumnal Parasite.—1. During the febrile period the small, more or less amoeboid, hyalin, intracorpuseular parasites are observed, from one-tenth to one-sixth the size of the red corpuscle.

2. During the afebrile stage the young pigmented forms are found in the blood.

3. Before the onset of a paroxysm, the pigmented forms are more numerous and have attained their largest size, about one-fourth of the infected corpuscle.

4. At the commencement of a paroxysm the parasites are generally remarkably few in number in the peripheral blood, but the young, unpigmented forms appear about the acme of the fever.

The Quotidian Estivo-autumnal Parasite.—The examination of the blood in the quotidian cases gives results substantially the same as those obtained in the tertian infections as given above, so far as the time of appearance of the parasites in the peripheral blood is concerned, so that it is unnecessary to repeat the data given.

In the irregular forms of estivo-autumnal fever it is often impossible to follow accurately the life-cycle of the parasites in the peripheral blood. Many of these forms are due to infections with more than one generation of parasites or double infections with the quotidian and tertian parasites or the benign tertian, and examination of the blood will, of course, be less satisfactory, as regards regularity in the presence of the organisms.

CHAPTER XIII

CLINICAL ILLUSTRATIONS OF THE QUOTIDIAN AND TERTIAN ESTIVO-AUTUMNAL FEVERS

IN the following chapter I have selected for description a number of typical cases of quotidian and tertian estivo-autumnal malarial fever which I have observed in soldiers returning from Cuba. I have selected these cases from hundreds of malarial patients because they were studied for several days before quinine was administered, and thus all the typical phenomena of the paroxysm were exhibited. From the charts shown it will be seen how the estivo-autumnal cases conformed to one of two types of fever, quotidian or tertian. In a previous contribution* I have shown how the estivo-autumnal malarial fevers present either quotidian or tertian paroxysms, and that each form is due to a distinct and characteristic form of malarial parasite. My observations confirm those of Marchiafava and Bignami, who were the first to describe the forms of the malarial parasites mentioned. They gave the names quotidian and malignant tertian estivo-autumnal parasites to the organisms described; but it would seem to be preferable to simply designate them as the quotidian and tertian parasites, as, in reality, the term "malignant" belongs rather to the quotidian than to the tertian form, as nearly all the pernicious cases of malaria which I have observed have been infected with the quotidian estivo-autumnal parasite.

I hope by the cases adduced to show the value of a careful study of our cases of malarial fever, both clinically and microscopically, and to demonstrate the occurrence of the two forms of the estivo-autumnal fever mentioned. I shall consider each case separately, giving the clinical history and describing the parasites found in the blood.

The cases are arranged as follows :

1. Cases of Quotidian Estivo-autumnal Fever.
2. Cases of Tertian Estivo-autumnal Fever.

*" Philadelphia Medical Journal," April 7, 1900.

In considering the subject in this manner, I have aimed to give the salient features, both clinical and microscopical, found in typical cases; but it should be understood that many cases occur which are not typical, where the temperature curve is more or less continuous; cases where there are mixed infections or infections with multiple groups of parasites, which it is impossible to describe in the limits of a chapter such as this. In such cases the clinical symptoms are often atypical and the temperature curves are most irregular and confusing. But no matter how typical a case of estivo-autumnal malaria we may have, it can be easily made atypical by the administration of small, broken doses of quinine. Such treatment—far too common—will cause the most typical temperature curve, whether quotidian or tertian, to become irregular and often altogether unrecognizable as one of malaria, and is the most prolific source of the existing confusion regarding the forms of estivo-autumnal fever. In combined infections with both the quotidian and tertian estivo-autumnal parasites, a more or less continued or slightly remittent temperature curve is seen, while in cases in which quinine in unsuitable doses, at irregular intervals, has been given, an irregular, intermittent temperature curve is most common. Where, however, no combination of the two varieties of the parasites exists, and quinine is not administered, it will almost invariably be found that either a quotidian or a peculiar tertian temperature curve will be observed.

CASES OF QUOTIDIAN ESTIVO-AUTUMNAL FEVER

There is nothing very peculiar about the temperature curve in this form of malarial fever, it very closely resembling an ordinary double tertian curve. It is a notable fact, however, that most cases of pernicious malarial fever which I have observed have presented this type of temperature curve, and the blood has shown the characteristic quotidian estivo-autumnal organisms. None of the cases described in this chapter were pernicious in character, as I have purposely selected those of a milder type, because they are so much more common.

CASE 1: CHART 6—HAMILTON.—The patient, a soldier, arrived at Santiago during August, 1898. He was there about one month when he was attacked by measles, which was followed

by dysentery. About the middle of October he began to have chills and fever. His chills occurred, as a rule, every day, but were sometimes irregular. Besides the chills, he suffered from nausea, vomiting, very severe headache and diarrhoea. Has had several attacks, followed by apparent recovery under treatment. He was feeling well on his arrival at the hospital, on June 23, 1899. Upon the 26th he began to run a temperature characterized by quotidian paroxysms, but had no distinct chill until the 30th. Up to the latter date he suffered from nausea, some headache and general pains. On the 30th he had a distinct chill, suffered from nausea, vomiting, sweating, severe frontal headache and general pain, especially severe between the shoulders. His bowels were constipated.

Physical Examination.—Patient is anemic and emaciated. Skin slightly yellow; face flushed; tongue heavily coated with a thick, yellowish fur and flabby; lungs and heart normal; pulse full and bounding; spleen enlarged and tender, reaching about 4 centimeters below ribs; liver normal. Some tenderness over abdomen on deep pressure, probably due to pressure on spleen.

Examination of the Blood.—The blood was examined daily at intervals until the parasites disappeared. It was found that they were the most numerous in the peripheral blood during or just after a paroxysm, but at no time were they numerous enough to show more than one infected corpuscle, on the average, to the field. The parasites were typical of the quotidian estivo-autumnal variety, and two forms were observed in the blood: the ring-forms and the pigmented forms. The ring-forms were very small, indistinct in outline, perfectly circular when at rest, and very actively amoeboid. They never showed any signet-ring appearance, and were never more than one-sixth the size of the infected corpuscle. Some infected corpuscles contained two and a few even three parasites. The pigmented forms were about one-fourth the size of the infected corpuscle, which was always shrunken, brassy green in color, and generally crenated. The outline of the organisms was much more sharply defined than it was in the case of ring-forms, and they were perfectly circular in shape, amoeboid motion having entirely disappeared. The pigment was in the form of one, or, at most, two rather large, almost black dots, either centrally or peripherally situated. The pigment was always entirely motionless. No segmenting forms nor crescents were observed in this case. The parasites disappeared from the

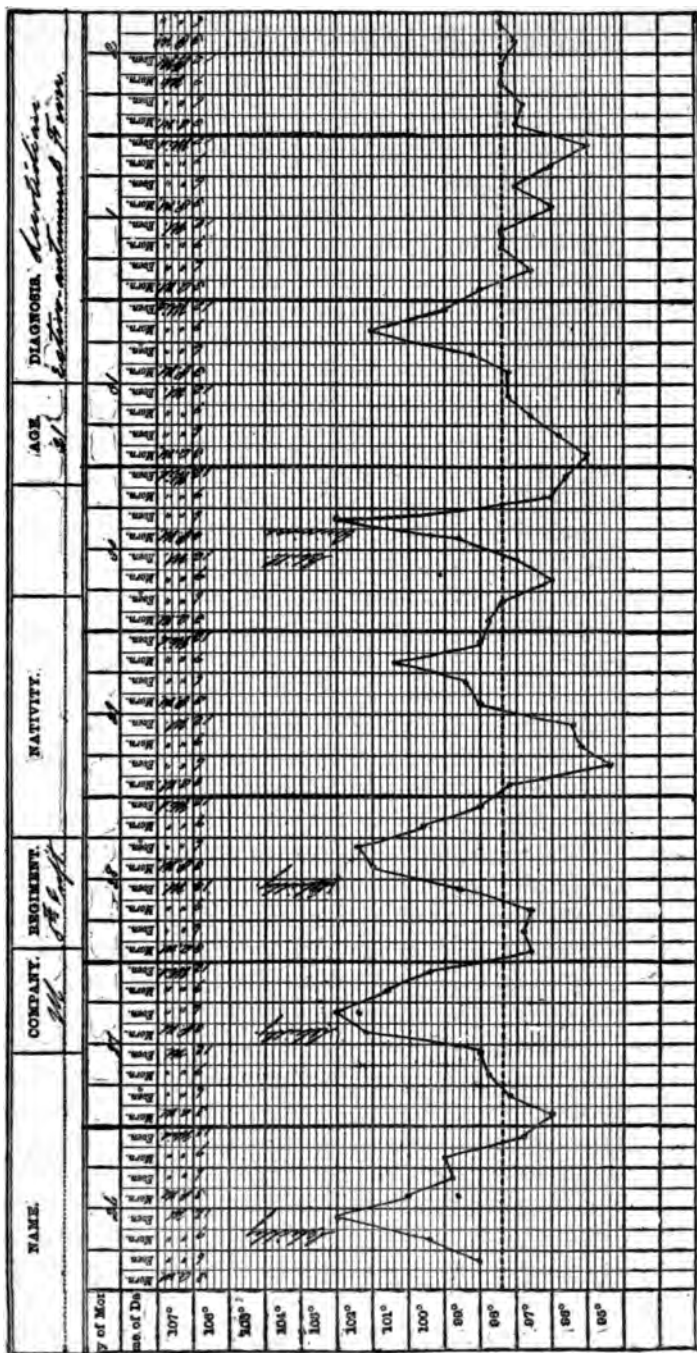


Chart No. 6. Quotidian Estivo-autumnal Malarial Fever.

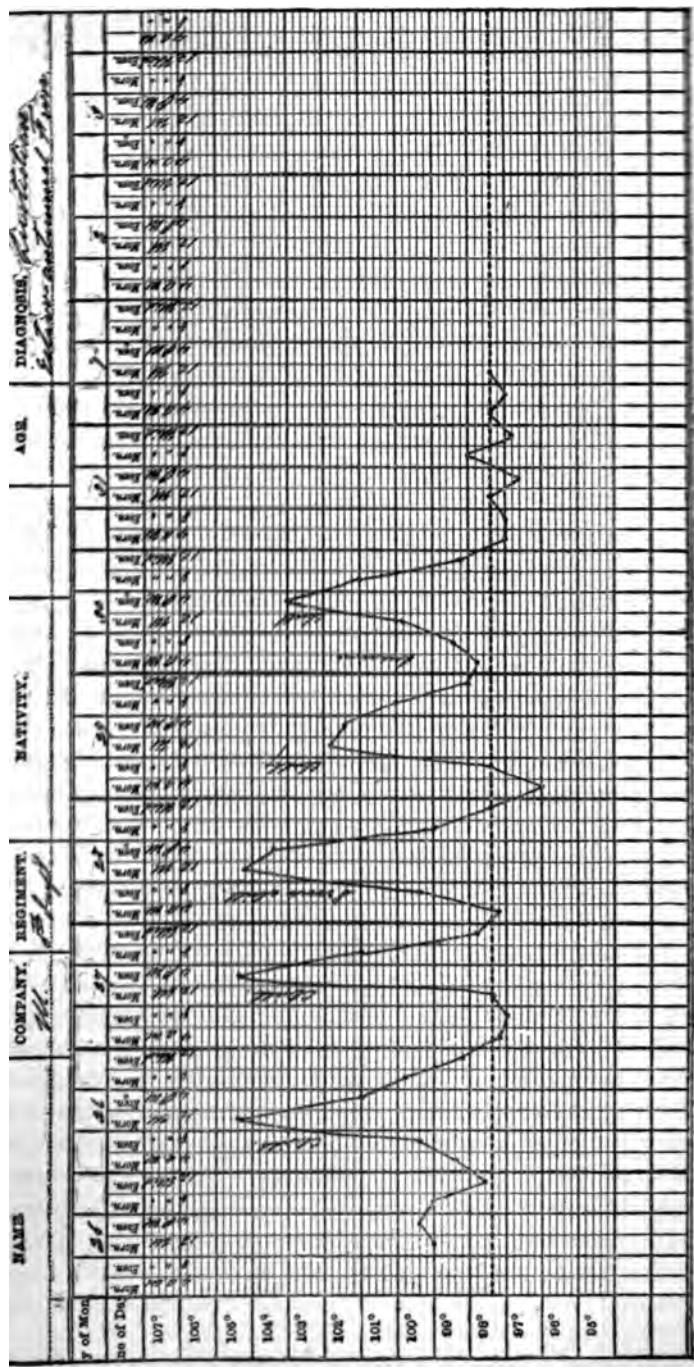


Chart No. 7. Quotidian Estivo-autumnal Malarial Fever.

blood two days after the commencement of the administration of quinine.

Treatment.—Quinine, in doses of .36, every four hours.

On reference to the temperature chart, it will be seen that there is nothing very distinctive about the temperature curve, beyond its quotidian character and the fact that during the first three paroxysms the patient felt slightly chilly, during the fourth even the chilly sensations were absent, and that the first distinct chill occurred during the fifth paroxysm. As far as the temperature curve is concerned, it might very well be that of a double tertian, the microscope alone being serviceable in differentiating the type of infection present. The temperature reached normal after two days' treatment with quinine. The subnormal temperature on the 29th, of 95.4° F., is worthy of notice, as it has been my experience that in no disease does the temperature so often reach low subnormal points as in the estivo-autumnal fevers.

CASE II: CHART 7—S. F. SHELTON.—The patient, a soldier, suffered for several weeks in Santiago, Cuba, from attacks of fever, accompanied by chilly sensations, headache, backache, slight nausea, and sweating. He grew gradually weaker and was transferred to the United States, arriving at the hospital on January 23, 1899. His temperature remained normal until the 26th, when he had a chill, which was repeated every day for four days. He suffered from severe headache, with much mental depression, nausea, backache, and darting pains down the legs.

Physical Examination.—Emaciated; skin of a peculiar grayish yellow hue; tongue thickly coated and flabby; expression listless and depressed; heart and lungs normal; pulse rapid, full and strong; spleen enlarged and tender, reaching about 6 centimeters below border of ribs; liver slightly enlarged; bowels constipated.

Examination of the Blood.—The blood was examined daily, at regular intervals, and showed very numerous quotidian estivo-autumnal malarial parasites. Ring-forms and pigmented forms were common, and on one occasion two segmenting forms were observed. The organisms were most numerous during the latter part of the paroxysms. The ring forms were very minute, indistinct in outline, and actively amoeboid at intervals. The pigmented forms were circular or oval in shape, and contained

one or two nearly black pigment dots. The pigment was immotile and the organisms showed no amœboid motion. The segmenting forms were both intracorpuseular, and in one instance the number of segments was six; in the other, eight. In one instance a peculiar double ring-form of the parasite was observed, which suggested a process of division. Numerous corpuscles were observed to contain two ring-forms.

Treatment.—Quinine .65 every four hours.

The temperature chart in this case shows an unusually high range of temperature for the quotidian estivo-autumnal infection, but is not otherwise remarkable. It resembles, even more than that of Case No. 1, an ordinary double tertian chart, and it would obviously be impossible to make a diagnosis of estivo-autumnal infection from the chart, without the aid of the microscope. The chart, is, however, a beautiful example of the temperature curve in the quotidian estivo-autumnal infections, as contrasted with the totally different temperature curve of the tertian type of the infection. It also shows how little a chart can be depended upon in making a diagnosis of the type of malaria present in a given case. It is safe to say that upon simple inspection, this, or, in fact, almost any quotidian estivo-autumnal chart, would be considered as a chart of double tertian malaria, and very justly so. The microscopical examination of the blood is the only means by which the diagnosis can be cleared up in such cases as these, and it should never be neglected, as it is of infinite importance to the patient whether or no he is suffering from the benign double tertian or the too often malignant estivo-autumnal infection. The prompt subsidence of so pronounced an infection, under large, repeated doses of quinine, is also worthy of attention.

CASE III: CHART 8—CECIL TAYLOR.—The history in this case is briefly as follows: The patient had never been in Cuba, and apparently his malaria was contracted at Fortress Monroe, as he gave no history of previous attacks. His illness began with a slight chill, nausea, vomiting, and severe headache and back-ache. He also had some abdominal tenderness and a slight epistaxis. His temperature reached 103.8° F. after the chill.

Physical examination showed an enlarged spleen, general abdominal tenderness, dry, hot skin, flushed face, injected con-

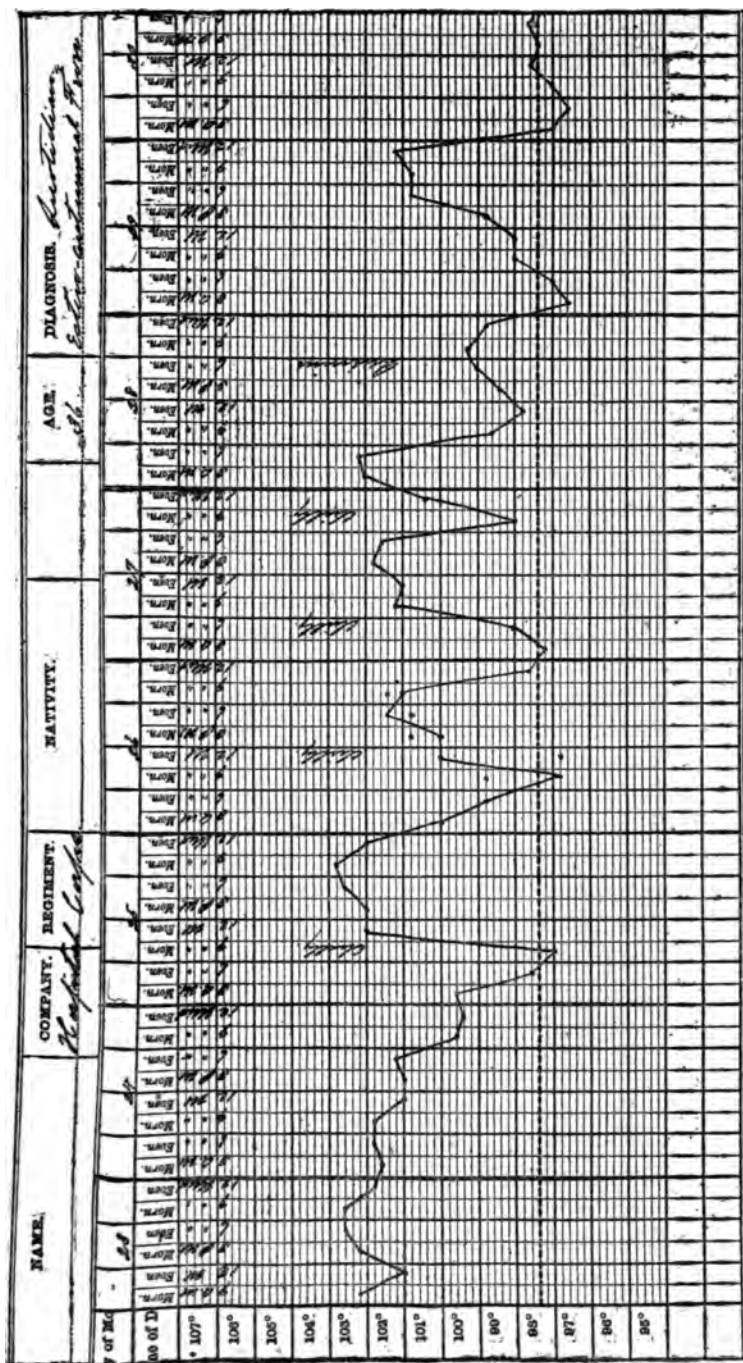


Chart No. 8. Quotidian Estivo-autumnal Malarial Fever.

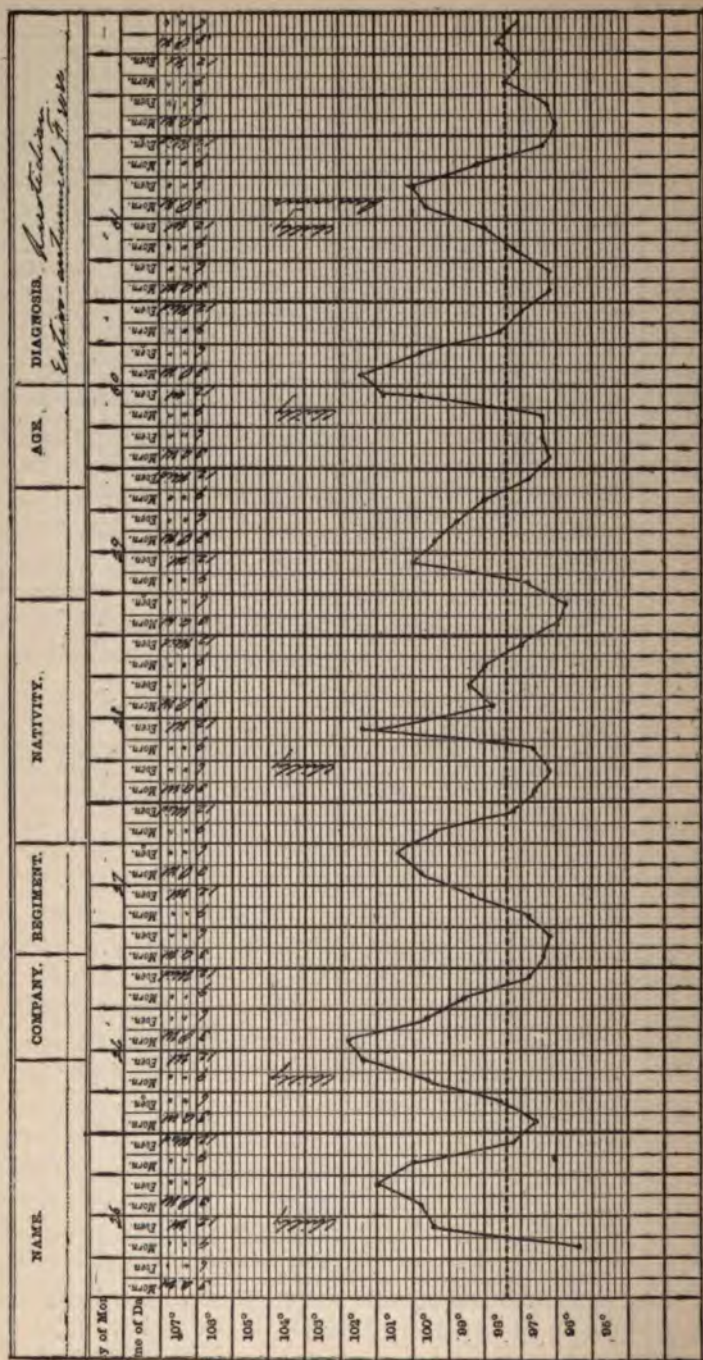


Chart No. 9. Quotidian Estivo-autumnal Malarial Fever.

junctivæ, and a pointed, tremulous tongue thickly covered with a white fur; the pulse full and rather slow. The case was regarded at first as one of typhoid fever, but no Widal reaction could be obtained, and examination of the blood showed large numbers of typical quotidian estivo-autumnal parasites.

Examination of the Blood.—The blood showed numerous intracorpuseular "ring-forms" of the estivo-autumnal parasites of the quotidian type, and also a few crescents. The intracorpuseular parasites were very small, rather dimly outlined, actively amœboid at times, and often corpuscles were seen containing two parasites. The infected corpuscles were smaller than normal, dark green in color, and often crenated. No pigmented forms were observed.

The crescents were remarkable because of their plump appearance and small size. They contained perfectly motionless, almost black pigment, in the form of short rods; their protoplasm had a peculiar refractive, ground-glass appearance, and in every instance a darker colored, greenish double outline was to be seen surrounding them. They were easily seen to be dissimilar from the more common tertian estivo-autumnal crescents.

Treatment.—Quinine, in .40 doses, given every four hours, caused a disappearance of the fever in two days.

In this case the temperature chart is not as typical as in the other cases cited, and is therefore more interesting. During the first two days of illness the temperature showed hardly any remission, but after that the remissions occurred as usual. It is difficult to explain this by any other hypothesis than a double infection, two groups of parasites reaching maturity within a few hours of each other. This explanation is further strengthened by the fact that on the 29th two paroxysms occurred; but this time the last paroxysm occurred after the remission of the first. As a whole, however, the chart is a fairly typical one of quotidian estivo-autumnal fever. It will be seen that the patient had no distinct chills, but chilly sensations.

CASE IV: CHART 9—ROBERT S.—Patient was forty years old and had been in the service for thirteen years; had always been well. Had had a slight cough at times during the past two years, but physical signs were negative. The sputum showed no tubercle bacilli. Was taken sick in Tampa, Florida, in 1898.

Had chills daily for three or four days. Recovered from this attack and went with his regiment to Santiago. He remained there until January, 1899, having several attacks of malarial fever and being unfit for duty about six weeks in all. Arrived at the hospital January 23, 1899. While here had a quotidian temperature and chilly sensations, with rarely a distinct chill. Suffered from headache, loss of appetite, pain in back and limbs, and slight nausea. Had no distinct sweats.

Physical Examination.—Patient somewhat emaciated and very anemic; skin bronzed and rather moist; tongue flabby and coated; spleen enlarged; heart and lungs normal; abdomen rather tender; pulse full and rapid.

Examination of the Blood.—The blood contained large numbers of ring-forms of the quotidian estivo-autumnal parasite and a few crescents. In several examinations only two pigmented parasites were seen.

The intracorpuseular rings were similar in appearance to those already described, being minute in size, rather dim in outline, and always perfectly round. The pigmented forms were circular in shape, more sharply outlined than the "rings," and the pigment consisted of one black dot situated in the center of the parasite. The pigment was perfectly motionless, and the parasites were not amœboid. The infected corpuscles were very dark green in color.

The crescents observed were small and very plump, and showed a double outline. An intracorpuseular crescent was observed during our examination.

Treatment.—Quinine, .40 doses every four hours reduced the temperature to normal very promptly.

The temperature curve in this case is remarkable for its regularity, and because of its resemblance to the temperature curve seen in pulmonary tuberculosis. This resemblance, together with an acute bronchitis present, caused the case to be considered as one of phthisis until the microscope cleared up the diagnosis, and quinine wrought a cure. The quotidian paroxysms, it will be noted, occurred with great regularity, and the temperature went below normal after each paroxysm. Without a blood examination it would be impossible, from the chart, to differentiate the two diseases, and it is in such cases as these that the value of a microscopical examination is shown. No distinct chills were

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In blood secured by puncture of the spleen, all stages of the development of this organism can be studied, and each stage differs markedly from the estivo-autumnal parasite causing paroxysms every forty-eight hours.

The points to be noted in the differentiation of the quotidian estivo-autumnal parasite are:

1. During its hyalin stage its minute size (about one-sixth of the corpuscle); its perfectly circular ring-shape; its very active amœboid motion, which occurs at intervals, and is so rapid that it must be carefully watched for; its indistinct outline at the earliest stage; the very dark green color of the infected corpuscle and its wrinkled or crenated appearance, and the fact that often more than one parasite occurs in a corpuscle.

2. During its pigmented stage its small size (about one-fourth of the corpuscle); its circular shape and loss of "ring-form" before pigmentation; its very sharply defined outline; its pigment, consisting of one or two coarse granules, perfectly motionless; its multiple occurrence in corpuscles, and their very dark green crenated appearance.

3. During segmentation, which takes place within the red corpuscles, and the number of segments is six or eight.

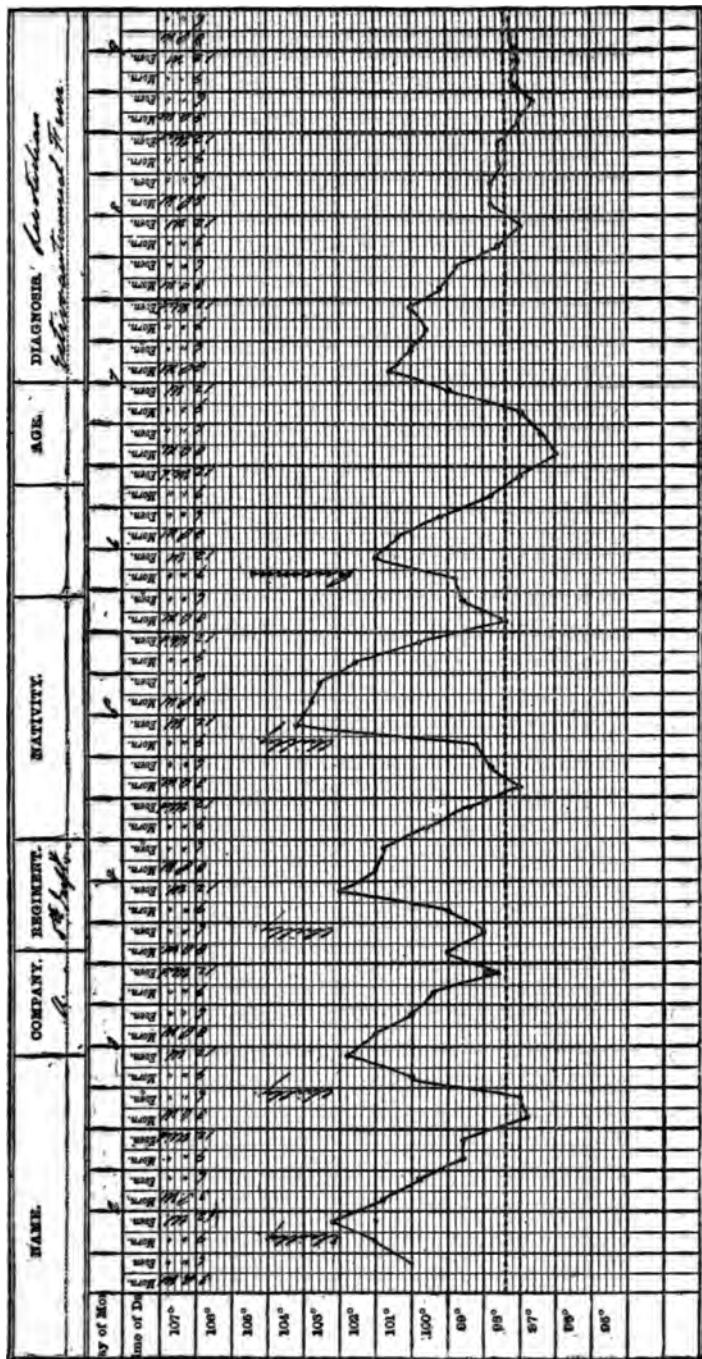
4. During phase of crescents which are small and plump, contain a small amount of pigment, and always show double outline.

5. The cycle of development, lasting twenty-four hours.

There is no difficulty in securing typical temperature charts of this form of malarial fever if quinine be withheld; but if it be given in small doses, or at long or unsuitable intervals, the regularity of the temperature curve is lost and, from a consideration of the chart, it becomes impossible to tell with what form of malaria we are dealing. To this is undoubtedly due the fact that this form of malaria has not been more generally recognized.

CASES OF TERTIAN ESTIVO-AUTUMNAL FEVER

In the chapters which have preceded this I have called attention to the fact that the majority of cases of estivo-autumnal fever present paroxysms occurring, approximately, every forty-



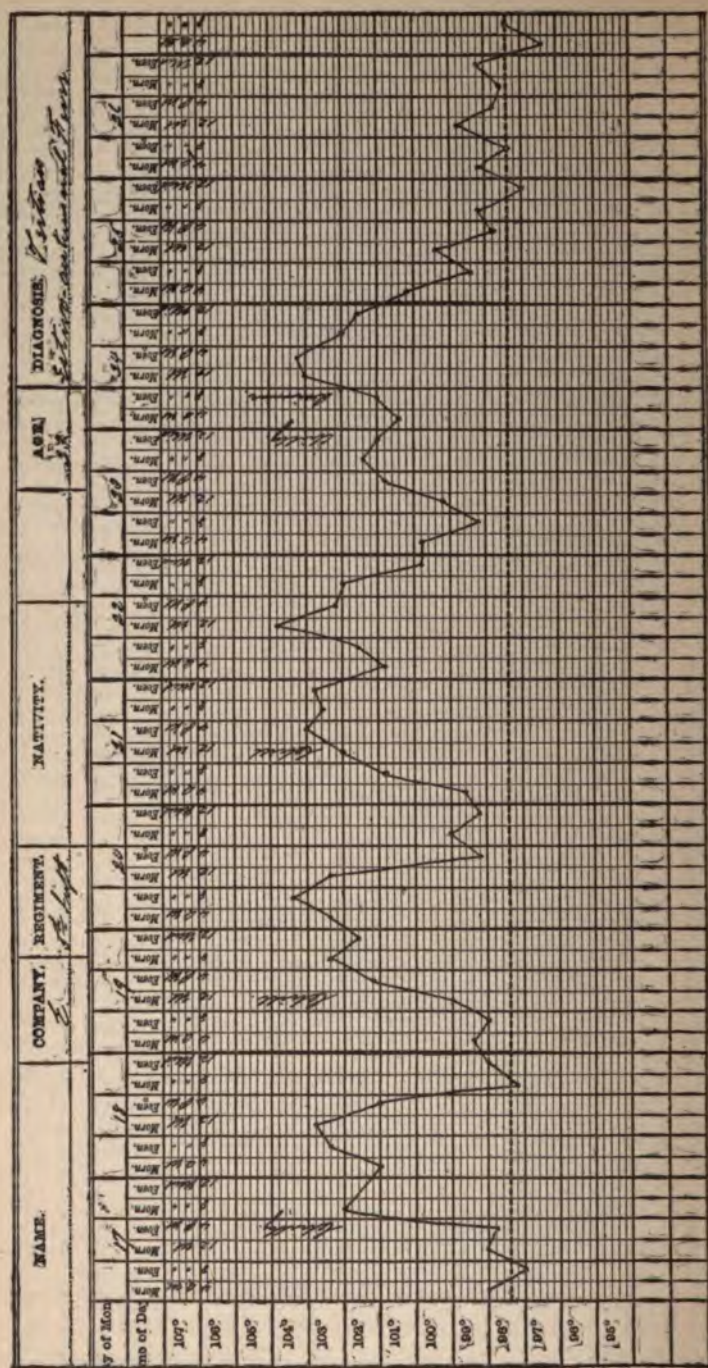


Chart No. 11. Tertian Estivo-autumnal Malarial Fever,

eight hours. These tertian paroxysms are peculiar in that while they occur every other day, each paroxysm is prolonged so that it lasts considerably over twenty-four hours, and often almost forty-eight hours. This type of malarial fever is further characterized by a peculiar temperature curve, which was first described by Marchiafava and Bignami. The analysis of the temperature curve in these cases shows the following characteristics: a rapid and sudden rise, a stage with slight remissions, a pseudocrisis, a precritical rise, during which the temperature reaches a higher point than it had previously, and, lastly, the true crisis, in which the temperature rapidly falls.

This peculiar temperature curve is presented in all uncomplicated cases of tertian estivo-autumnal fever, where quinine has not been administered. In cases which are infected by two groups of the parasites ripening at different periods, or by the tertian or quartan parasites, or, again, by both the quotidian and tertian estivo-autumnal parasites, this peculiar temperature curve will not be exhibited, nor will it be in cases which have received small doses of quinine or quinine at long intervals.

In order, then, to secure a typical temperature chart of the tertian estivo-autumnal fever, we must have a patient infected by a single group of parasites, and must withhold all quinine for several days. It is safe to say that all the confusion existing to-day regarding the types of estivo-autumnal fever is due to one of two factors, infection by more than one variety of malarial parasite, and the improper and untimely administration of quinine. The first factor can only be eliminated by the use of the microscope in diagnosis, and the second only by an earnest scientific spirit on the part of the physician, so strong that he will be willing to withhold quinine long enough to secure a proper knowledge of the character of the case which he is called upon to treat. Medicine, to-day, has reached a stage where the so-called diagnostic terms of "remittent" and "intermittent" malarial fevers are of little exact meaning; and earnest effort should be made to substitute for them, in medical nomenclature, the more scientific terms, tertian, quartan, and quotidian and tertian estivo-autumnal malarial fevers.

The following cases are selected from a large number because they are typical of the tertian estivo-autumnal fever, and because they presented all forms of the tertian estivo-autumnal parasite, for this form of malarial fever is dependent upon a character-

istic parasite, possessing well-recognized differences from the parasite causing the quotidian form of the fever, and which is easily differentiated by the microscope, when one has become accustomed to the appearances presented by it in the blood.

From the following cases, in which I have especially considered the character of the temperature curve and the parasites present, I hope to prove conclusively the occurrence and distinct character of the tertian form of estivo-autumnal fever:

CASE I: CHART 11—SIDNEY C.—Age, 23. The patient arrived at Santiago, Cuba, in August, 1898. On September 20, 1898, he was taken sick with a chill, which was followed by a high temperature. He had chills every other day for several days, and suffered from nausea and vomiting, severe headache and legache, and drenching perspiration. He had several attacks during the next two months and was finally sent to the Simpson hospital, where he arrived on December 11, 1898. On December 17 he had a rise of temperature, accompanied by chilly feelings. This paroxysm was succeeded by three others, all accompanied by severe headache and backache, nausea, and great nervous prostration.

Physical Examination.—Patient somewhat emaciated; skin yellowish; mucous membranes pale; cheeks flushed; eyes bright; tongue broad and coated; heart and lungs normal; abdomen rather tender; bowels constipated. Marked mental depression and general debility.

Examination of the Blood.—The blood was examined at frequent intervals, and numerous ring-forms, pigmented rings, and larger pigmented forms of the tertian estivo-autumnal parasite were found. No segmenting forms were observed. The "ring-forms" were larger than those of the quotidian parasites, being about one-fourth the size of the infected corpuscle, irregular in shape, most of them presenting an enlargement at some portion of their periphery, thus causing the so-called "signet-ring" appearance. They were very refractive and sharply outlined, looking as though they were cut or stamped into the corpuscle; the protoplasm was clear and the amœboid movements were sluggish. The "ring-form" was sometimes lost, a clear, circular hyalin disk resulting. No corpuscles were observed to be infected by more than one parasite, and the corpuscle itself, although more greenish in color than the uninfected ones, was very much less

altered in appearance than in the quotidian infection, and but seldom crenated.

The pigmented rings and pigmented bodies were present in small numbers. The pigmented rings showed a few fine pigmented granules, generally in the dilated portion of the ring, and these granules were often in rapid motion. These pigmented rings still showed amœboid motion, sometimes very noticeable.

The pigmented parasites were larger than the rings, being nearly one-half as large as the infected corpuscle; they were very sharply defined, the protoplasm being very refractive and finely granular in appearance. The pigment was in the form of fine reddish brown granules, and had a marked vibratory motion. The amœboid motion of these parasites was very sluggish, and in some had entirely disappeared.

Treatment.—Quinine, .40 every four hours, reduced the temperature in two days, and its continued use resulted in recovery.

A consideration of the temperature chart in this case shows a beautiful illustration of the peculiar temperature curve in this type of malarial fever. Quinine was withheld until the occurrence of the fourth paroxysm. It will be seen that the paroxysms occurred at intervals of forty-eight hours approximately, and that they lasted from thirty-six to forty-eight hours. It also shows well the several characteristics of the curve noted before. Taking the paroxysm of the 21st for example, we see beautifully illustrated the rise, the period of slight remissions, the pseudocrisis, the precritical rise, in which the temperature reached the highest point, and, lastly, the crisis, in which the temperature gradually returned to normal. The intervals between the paroxysms were short, as shown by the chart. It will also be noted that two of the paroxysms were accompanied only by chilly feelings, while two commenced with distinct chills. As a general rule the temperature goes to normal or below, during the intervals, but in this case it did not.

CASE II: CHART 12—PAUL R. H. — Age, 21. Patient arrived in Cuba on December 17, 1898. Was taken sick March 13, 1899, with severe pain in the head, chill, high fever, and nausea, and vomiting. Was supposed to be suffering from typhoid fever, but felt better after a week in the hospital and

was up and about. On April 6, the day before he boarded the steamer on his way to Fortress Monroe, the fever returned, accompanied by the same symptoms. Arrived at the Simpson hospital on April 12. Since arrival he has had four chills, occurring every other day, but not very severe, accompanied by nausea, vomiting, headache, high temperature, and pain in the back and legs.

Physical Examination.—Patient looked very ill. Greatly emaciated, skin yellow, cheeks flushed, eyes bright, tongue broad and coated with yellowish fur. Heart and lungs normal. Pulse rather weak. Spleen slightly enlarged. Liver normal. Abdomen rather tender. Bowels constipated.

Examination of the Blood.—The blood was examined at frequent intervals and always showed numerous ring-forms and pigmented rings of the tertian estivo-autumnal parasite, similar in every respect to those described in Case I. No segmenting forms or crescents were found in the peripheral circulation. The parasites were most numerous just before the paroxysms.

Treatment.—Quinine, .50 every six hours. Recovery.

The temperature chart in this case is a typical one of the tertian estivo-autumnal fever. It will be seen that there were four paroxysms in all, and that each of them showed the characteristic temperature curve, although the paroxysm of the 23d is slightly atypical, in that after the pseudocrisis there occurred a slight remission before the final rise and the crisis. That of the 27th is very typical. In no other malarial disease will a temperature chart like this be seen, and it is actually diagnostic of the type of infection present.

CASE III: CHART 13—A. H. HALL.—The patient, while in Santiago, suffered from malarial fever, having chills nearly every other day, accompanied by high fever, severe headache, backache, and nausea. Arrived at Fortress Monroe on January 23, 1899. Has had several paroxysms of fever, accompanied by chilly feelings, but no distinct chill, severe headache, and backache, some nausea, and general muscular pain.

Physical Examination.—The patient showed but little emaciation and appeared physically well. There was some anemia, the tongue was coated, the bowels constipated. Heart, lungs, and spleen apparently normal. The spleen was enlarged, reaching half



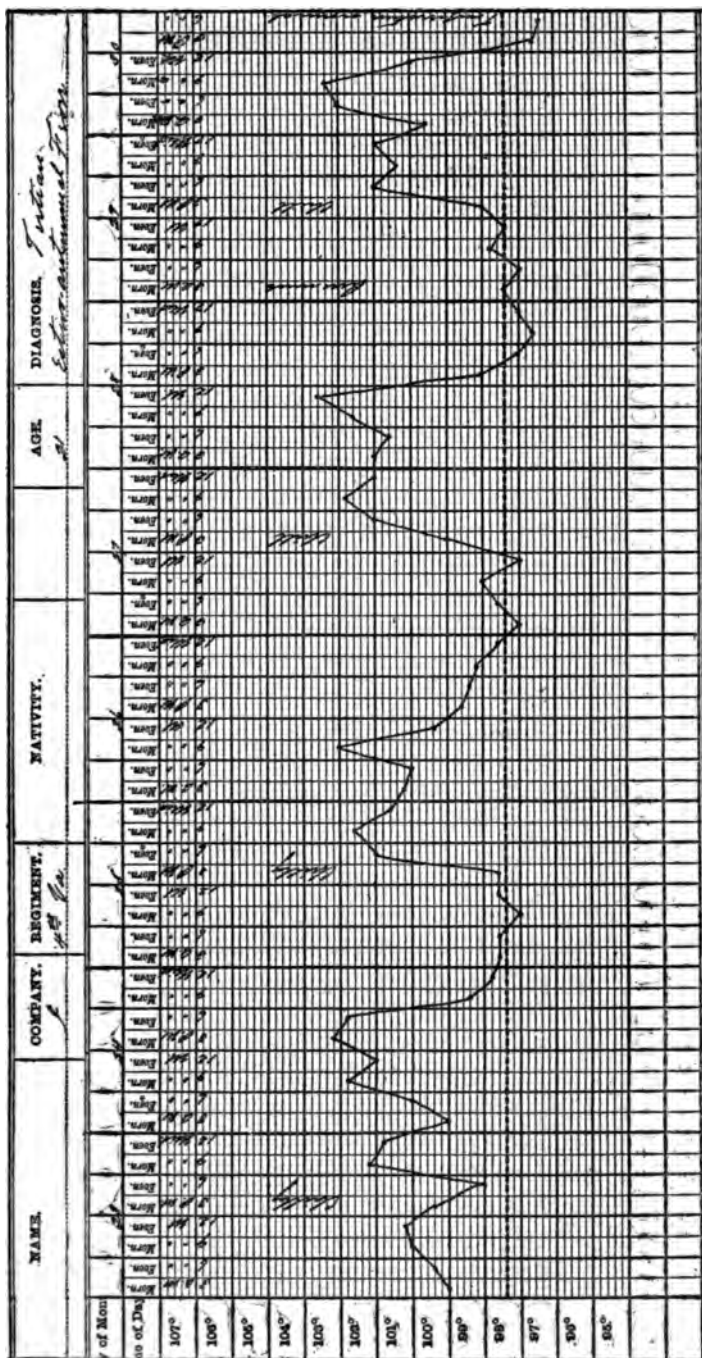


Chart No. 12. Tertian Estivo-autumnal Malarial Fever.

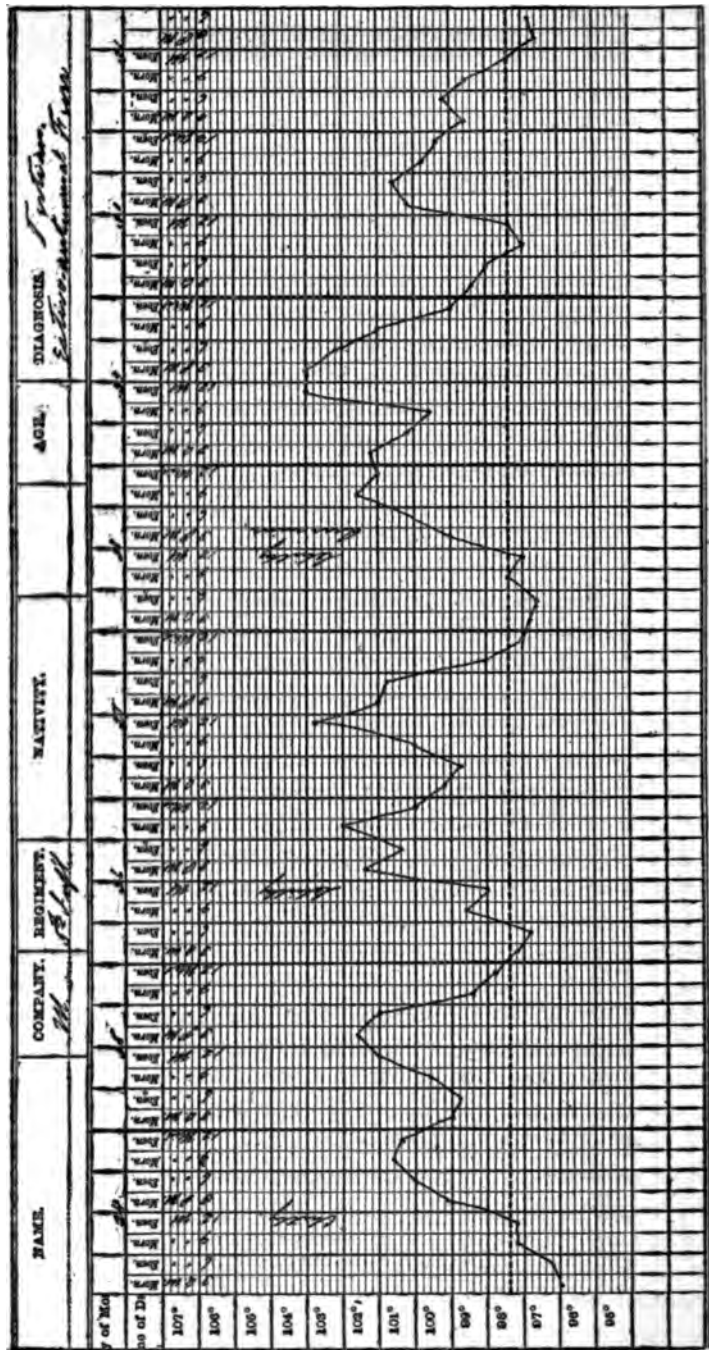


Chart No. 13. Tertian Estivo-autumnal Malarial Fever.

way to the umbilicus. There was much mental depression present. Pulse full and regular.

Examination of the Blood.—The blood was examined frequently and numerous pigmented and unpigmented tertian estivo-autumnal parasites were found, most numerous just before or some time after a paroxysm.

Treatment.—Quinine, .40 every four hours. Recovery.

In this case the temperature chart is again typical of the tertian estivo-autumnal infection, and would easily be recognized on simple inspection. The occurrence of the paroxysm on every third day, the length of the individual paroxysm, the peculiar curve exhibited, all prove conclusively the type of malarial disease present, even without the aid afforded by the microscope in detecting the characteristic parasite.

CASE IV: CHART 14—SULLIVAN.—The patient arrived at Santiago in August, 1898. Was there about two weeks when he was taken suddenly ill, having a chill, high fever, nausea and vomiting, and great mental depression. Chills recurred every third day, and were always accompanied by intense headache and fever. Arrived at Simpson hospital on December 11, 1899, and on the 16th had chilly sensations and a rise of temperature. He had two paroxysms after this, accompanied by fever, intense headache, nausea, general muscular pain, and mental depression.

Physical Examination.—Patient appears well, save for some anemia and listlessness. Skin is slightly yellow, tongue slightly coated. Heart, lungs, and liver apparently normal. Spleen not appreciably enlarged. Bowels constipated. Pulse full and regular.

Examination of the Blood.—Numerous examinations of the blood were made, and pigmented and unpigmented ring-forms of the tertian estivo-autumnal parasites were found as well as large pigmented forms. Several segmenting forms were observed.

The pigmented and unpigmented ring-forms have already been described under Case I. The large pigmented parasites were nearly half as large as the infected corpuscle, and contained numerous fine granules of pigment, generally collected near the center of the organism. The parasites were very sharply cut and refractive. In some of the pigmented forms the pigment was collected in a solid block at the center, and

faint radial striations could be made out dividing the organism into several segments.

The segmenting forms observed were extracorpuseular, and consisted of blocks of pigment with ten or more oval segments arranged around them. The segments were very minute.

Treatment.—Quinine .40 every four hours. Recovery.

The temperature chart in this case is interesting in that each of the three paroxysms presents a modification of the typical tertian estivo-autumnal curve. In the first paroxysm there is no stage of slight remissions, there being a rapid initial rise and almost immediately a pseudocrisis, in which the temperature reached normal. This was immediately succeeded by the precritical rise and followed by the crisis.

In the second paroxysm there is also no stage of slight remissions, but the pseudocrisis is more normal and the precritical rise more gradual.

The third paroxysm is marked by a well-defined stage of slight remissions, but the pseudo-crisis is almost absent.

Such slight modifications as these are very common in tertian estivo-autumnal cases, but they do not in the least affect the general character of the temperature curve, nor cause a moment's doubt as to the nature of a case showing such a temperature curve as is here presented. Such temperature curves are uniquely characteristic of, and are only associated with, the tertian estivo-autumnal infections.

CASE V: CHART NO. 15—CHARLES CONNOR.—Age, 25. Arrived at Santiago, Cuba, in August, 1898. Was there about one month, when he had a sharp chill followed by high temperature. Chills occurred for a while on every third day, but later became irregular. They were always followed by a high temperature. He was admitted to the hospital there five different times, each apparent recovery from the fever being followed by a relapse as soon as he returned to duty. During the paroxysms he suffered from very severe headache, muscular pain, nausea, and vomiting. He arrived at the Simpson hospital on December 11, 1898. Had chilly sensations and headache on the 15th, followed by a rise of temperature. He had three slight paroxysms afterward, accompanied by slight chilly sensations.

Physical Examination.—Patient emaciated and anemic. Skin

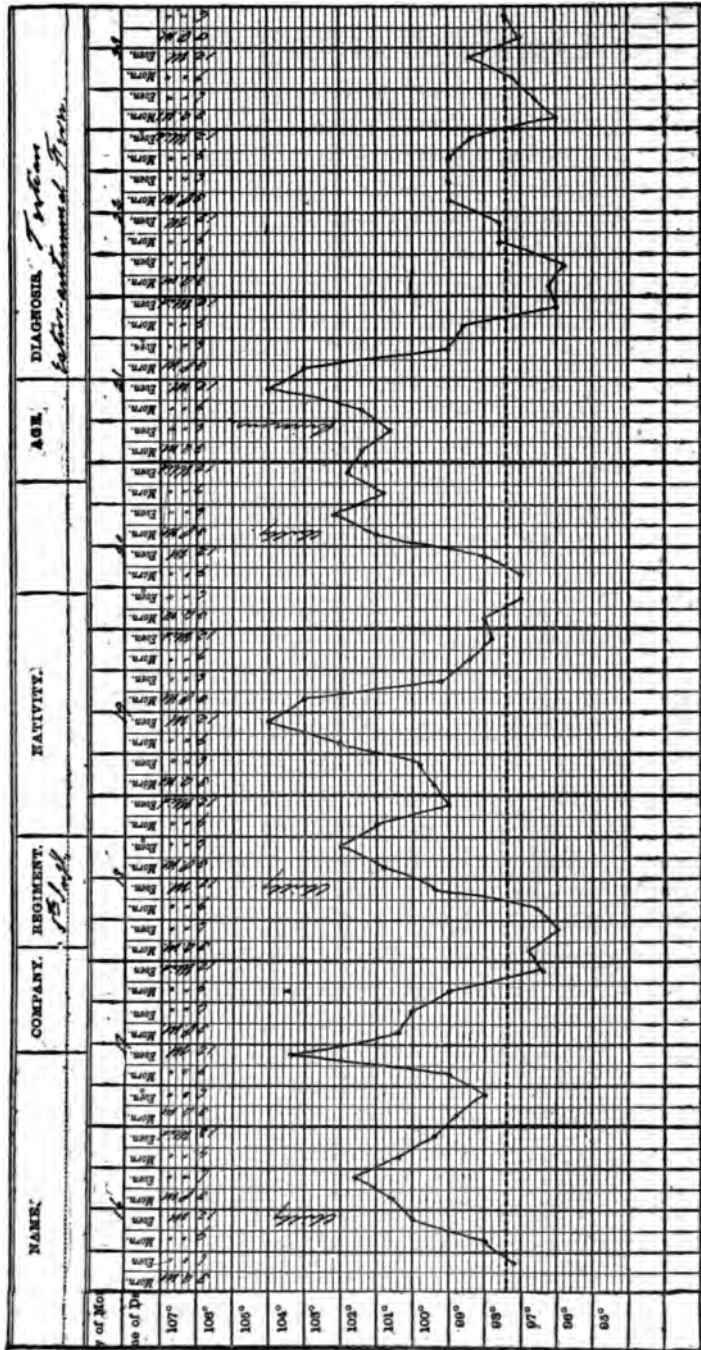


Chart No. 14. Tertian Estivo-autumnal Malarial Fever.

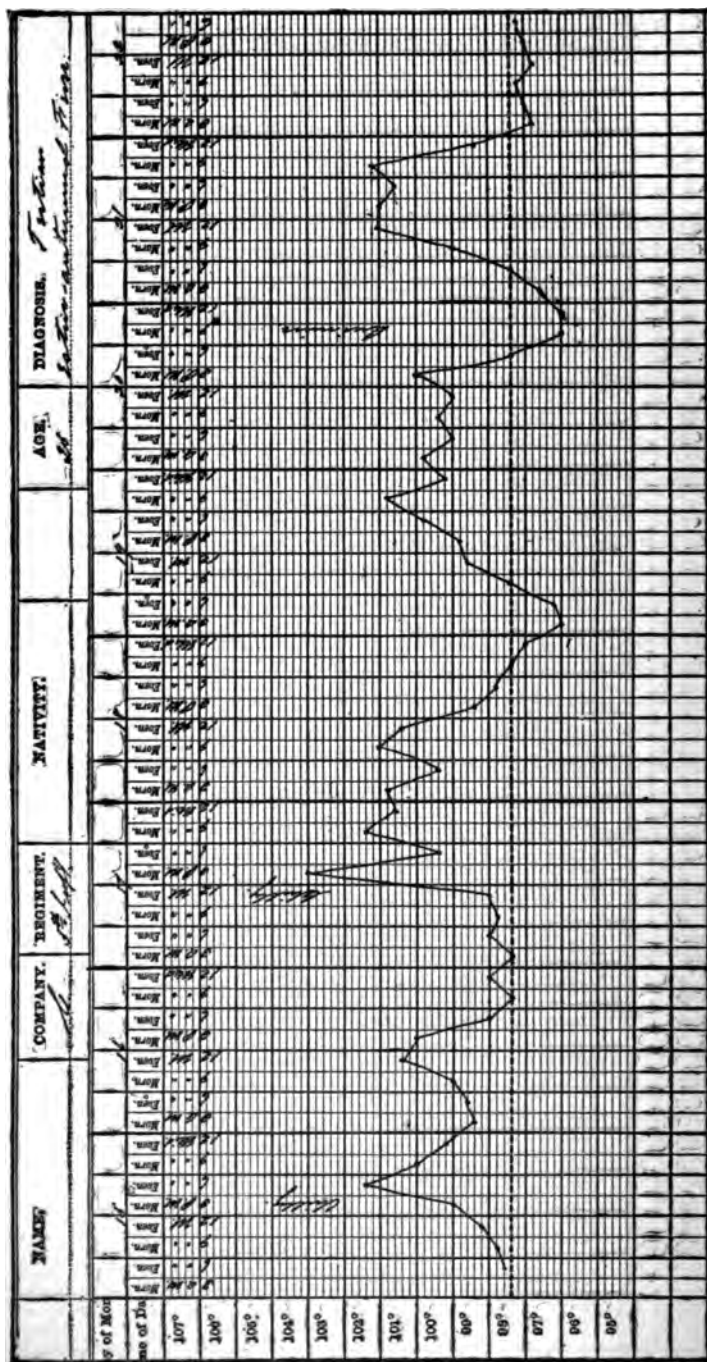


Chart No. 15. Tertian Estivo-autumnal Malarial Fever.

yellow, tongue flabby and coated. Heart and lungs normal. Spleen greatly enlarged, reaching nearly to the umbilicus. Liver dullness normal. Bowels constipated. Abdomen tender.

Examination of the Blood.—The blood in this case showed numerous pigmented ring-forms. Tertian estivo-autumnal The ring-forms have

tender and larger than parasites, and contained color. The double outline crescents were more

not as typical as the more chronic form of paroxysms occur every will be noted that the that there seems to be of the infection. The a reversal of the ordinary temperature being reached chart the temperature that a diagnosis of be made from an

estivo-autumnal malaria no differentiation is symptoms, save that ons occur every day, ay. A consideration such a marked difference admit that we are tion. The quotidian remittent temperature an, while the tertian ar and characteristic that shown in any in itself. When to is due to a distinct hown, the conclusion tivo-autumnal fever,

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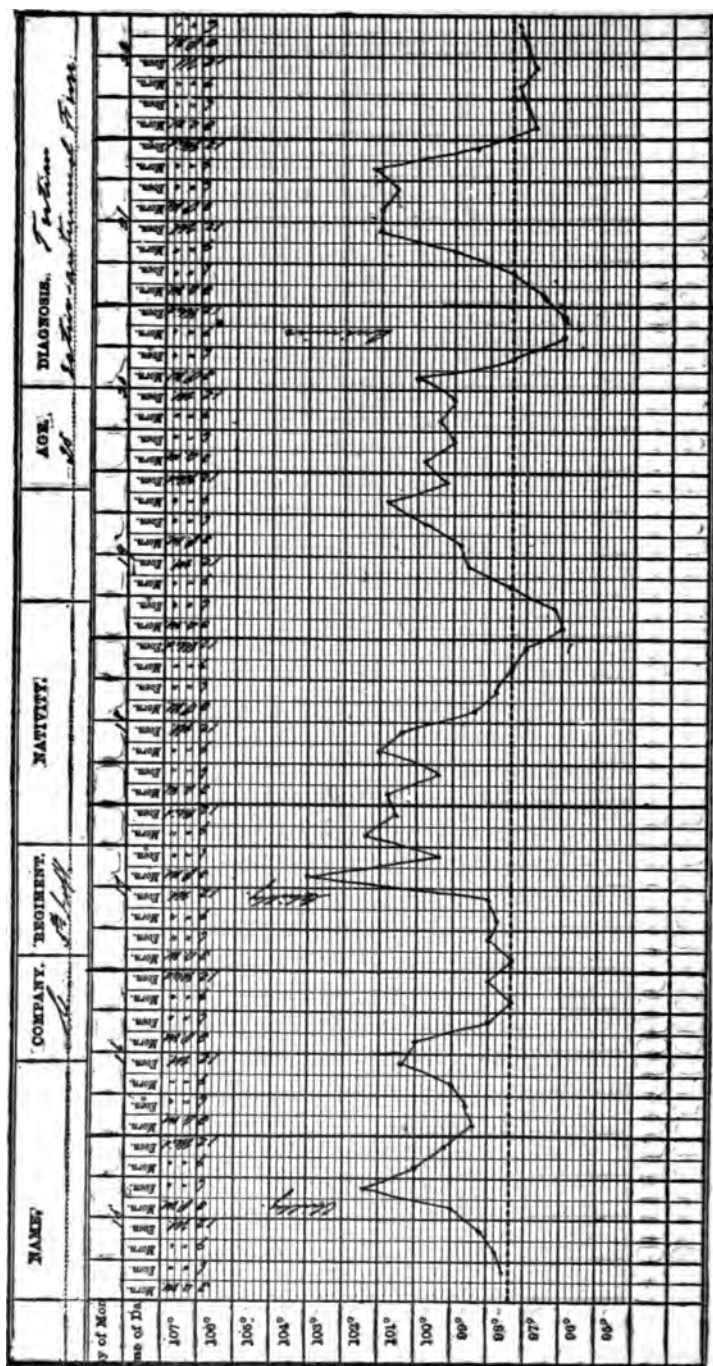


Chart No. 15. Tertian Estivo-autumnal Malarial Fever.

yellow, tongue flabby and coated. Heart and lungs normal. Spleen greatly enlarged, reaching nearly to the umbilicus. Liver dullness normal. Bowels constipated. Abdomen tender.

Examination of the Blood.—The blood in this case showed numerous pigmented ring-forms of the tertian estivo-autumnal parasite and also numerous crescents. The ring-forms have already been described under Case I.

The crescents were very much more slender and larger than those of the quotidian estivo-autumnal parasites, and contained much more pigment of a more reddish color. The double outline was much less common, but the tertian crescents were more refractive.

In this case the temperature chart is not as typical as the preceding ones, but it is typical of the more chronic form of the tertian estivo-autumnal infection. The paroxysms occur every forty-eight hours approximately, but it will be noted that the range of temperature is not as high and that there seems to be a tendency toward a spontaneous decline of the infection. The chart is curious in that there seems to be a reversal of the ordinary temperature curve, the highest temperature being reached during the initial rise; but even in this chart the temperature curve is, on the whole, so characteristic that a diagnosis of tertian estivo-autumnal fever could easily be made from an inspection of it.

From the cases of quotidian and tertian estivo-autumnal malarial fever considered it will be seen that no differentiation is possible from a consideration of the clinical symptoms, save that in the first-named the chill or chilly sensations occur every day, while in the latter they occur every other day. A consideration of the temperature charts, however, shows such a marked difference in the temperature curve that we must admit that we are dealing with two distinct types of infection. The quotidian estivo-autumnal type shows a simple intermittent temperature curve, indistinguishable from a double tertian, while the tertian estivo-autumnal type presents a most peculiar and characteristic temperature curve, entirely different from that shown in any other type of malarial fever, and diagnostic in itself. When to this is added the fact that the tertian form is due to a distinct and easily differentiated parasite, as I have shown, the conclusion is inevitable that there are two varieties of estivo-autumnal fever,

the quotidian and tertian, and that each is due to a characteristic parasite, as first shown by Marchiafava and Bignami.

The tertian estivo-autumnal parasite differs from the quotidian parasite in the following particulars:

1. During the hyalin stage the rings are large, being from one-third to one-fourth the size of the infected corpuscle; the signet-ring shape; the sluggish amœboid motion; the clear-cut and refractive outline, which is not so distinctive after the quotidian parasite has developed for some hours; the less wrinkled and lighter green infected corpuscle; the occurrence of only one parasite in the infected corpuscle.

2. During the pigmented stage, larger size, one-half of the corpuscle; the pigmented ring-forms; the continuance of amœboid motion; more sharply defined and refractive; the granular protoplasm; the finely granular pigment, which is motile; the occurrence of only one parasite in a corpuscle, and the lighter-colored, seldom-crenated infected corpuscle.

3. During the segmenting stage, the occurrence of segmentation outside the corpuscle; the number of segments, ten to fifteen.

4. The larger, more narrow, more deeply pigmented crescents.

5. The cycle of development—forty-eight hours.

These morphological differences considered together with the totally different temperature charts should be sufficient to distinguish the tertian from the quotidian type of estivo-autumnal malaria, and I am satisfied that careful study will confirm in every detail the truth of the existence of the two types of fever described.

CHAPTER XIV

THE PERNICIOUS FORMS OF THE ESTIVO-AUTUMNAL MALARIAL FEVERS

IN this chapter I shall describe the pernicious forms which the estivo-autumnal malarial fevers sometimes assume. It should be distinctly understood that there is no parasite which produces *only* pernicious malarial fever, but that the same parasite which causes the mildest estivo-autumnal infection is also capable of causing the most rapidly fatal form. As the vast majority of fatal cases of malarial fever are due to the estivo-autumnal parasites, it is at once easily seen how important it is to be able to differentiate them. Any malarial fever may suddenly develop malignancy and cause the death of the person infected; hence the absurdity of trying, as some authors have, to classify such cases as disease entities, dependent upon a peculiar and special parasite.

The great majority of pernicious attacks of malaria, in the northern altitudes, occur in the summer and autumn, and are rare, while in the tropics they occur throughout the year and are common. Most pernicious attacks of estivo-autumnal fever occur in patients who have previously suffered from severe paroxysms, which have not been properly treated, and the pernicious symptoms often develop during such a paroxysm.

Why do certain cases develop pernicious characteristics? Bastianelli and Bignami have carefully studied the development of such cases and have come to the following conclusions:

"The conditions through which a malarial fever becomes pernicious are:

"I. That the infection be produced by one of the varieties of the estivo-autumnal parasite. [This condition will not hold, as several authorities have observed pernicious cases due to the tertian parasite.]

"II. The second condition relates to the abundance of the parasites, and it may be stated as follows: In pernicious fevers, if one take into consideration not only the examination of blood

from the finger, but also the condition in the vessels of the various organs, it is a striking point that, however the distribution of the parasites may vary in individual cases their total number is always considerable. As regards the distribution, one may make the following distinctions. There exist:

"1. Cases in which the number of parasites is most abundant, yes, enormous, in the brain, while all the organs are less uniformly invaded. These are the commonest forms of pernicious fever, and are usually accompanied by coma.

"There are some cases in this category in which the number of parasites in the blood of the finger, of the spleen, of the bone marrow, etc., is enormous, while the number in the brain is scanty. Clinically, the absence of cerebral phenomena is noted.

"2. Cases in which the number of organisms is absolutely and relatively scanty in the bone-marrow, in the spleen, and in the liver, while they may be relatively few in the blood of the finger, and yet other organs are crowded with the parasites. Among these the following localizations are to be made out:

"a. The brain and the meninges are filled with parasites, either in sporulation or in all their stages of development. Clinically, there are cerebral phenomena.

"b. The stomach and intestines are chiefly invaded. In these organs the mature forms of the parasite are usually found: these are the cases of pernicious fever which present clinically intestinal phenomena."

Besides the reasons above given, it is probable that the amount of toxins secreted by the parasites have much to do with the production of pernicious symptoms, as well as the physical condition of the infected individual and his surroundings as regards climate, food, hardships, etc.

The pernicious forms of estivo-autumnal fever are classified in two ways, i. e., from the character of the temperature curve, and from the most prominent symptoms present.

Under the first classification we may have *tertian*, *quotidian*, *remittent*, or *lucral* pernicious fever.

Under the second classification we may have *comatose*, *delirious*, *litanic*, *clamptic*, *hemiplegic*, *bulbar*, *ataxic*, *dysenteric*, *choleraic*, *algid*, *cardialgic*, *diaphoretic*, *hemorrhagic*, *pneumonic*, and the *bilious* pernicious fevers.

Pernicious attacks are sometimes very rapidly fatal, while at others they are more gradual in their course. As a rule, the per-

nicious symptoms develop gradually, but sometimes very abruptly. The coma may strike the patient like a lightning-flash, death following shortly, or it may persist for several days.

DESCRIPTION OF THE MORE COMMON FORMS OF THE PERNICIOUS ESTIVO-AUTUMNAL MALARIAL FEVERS

The Comatose Form.—(Apoplectic form.) This is the most common form of pernicious malarial fever and occurs in two ways: either as a sudden attack or as a gradually developing comatose condition during an attack of the fever.

The sudden development of coma is rare, and, unless at once recognized and properly treated, almost invariably fatal. In this form the patient, who has not felt unwell enough to cease his occupation, is suddenly stricken with a profound coma, falls to the ground and, in the fatal cases, does not again regain consciousness. The face is suffused, the pupils contracted, the respirations hurried and labored, the pulse at first full and bounding, later soft, rapid, and thready. Such attacks, if untreated, seldom last over two days. This form of pernicious malaria is very often taken for apoplexy, and the microscopical examination of the blood is the only method to be relied upon in making a diagnosis, as the temperature is irregular, seldom reaching 103° F., and often subnormal.

The Typical Comatose Form.—In this, the most common form of pernicious malaria, the coma develops more or less gradually during an attack of the fever. The attack begins usually with a slight chilly sensation, languor, nausea, or vomiting, severe headache, and a rise of temperature. In some cases a marked nervous condition is present, and even delirium may precede the coma. As a rule the patient is restless and mentally depressed. Following this there develops a tendency to somnolence, which deepens into stupor and finally coma. The unconsciousness is complete and the patient lies either perfectly quiet or there are restless movements of the arms and legs. The skin often assumes an icteric hue and is hot and dry; the pupils are generally equally contracted, but may be unequally or equally dilated. The icteric hue may be very noticeable in the conjunctivæ, this symptom, in infected regions, often leading to a diagnosis of yellow fever. The face, when the malarial infection is of recent origin, is flushed and may be cyanotic; in old infections the face may

be pale; slight spasms of the muscles of the face are not infrequent. The tongue is tremulous, dry, and thickly coated. The occurrence of slight hemorrhages into the skin is sometimes observed. There may be hemiplegia present, or even total paralysis. The patellar reflex may be absent or slightly increased. The respirations may be slow and quiet, interrupted, or rapid and stertorous. The Cheyne-Stokes type of respiration is sometimes observed. The pulse is generally slow and full and incompressible at first, but becomes rapid and weak as the paroxysm progresses. As a rule the feces and urine are passed involuntarily, but in some cases retention of urine occurs.

The duration of the coma is variable, lasting from a few hours to three or four days. As a rule it does not persist longer than twenty-four or thirty-six hours.

In cases having a fatal termination the pulse becomes thready, rapid, and intermittent; the respiration irregular, labored, or shallow; the skin pale and bedewed with cold perspiration, and death occurs. In cases which recover the temperature falls, accompanied by perspiration, the consciousness is slowly regained, preceded usually by a quiet sleep.

In many cases this improvement is only apparent, and the patient relapses, in a few hours, into a second paroxysm, and from this, even into a third, which usually results fatally. Between the paroxysms the mental condition is one of torpor or great mental depression, accompanied by severe cephalgia.

Sometimes following the coma a condition of active delirium develops which may endanger the patient's life.

As regards the temperature in this form of pernicious malarial fever, it may be said that it is irregular. Some cases present a high temperature throughout, between 103° and 105° F., while in others the temperature remains mostly normal, or below that. In fatal cases the fever, if present, declines some hours before death; in other cases it ascends, and Manson cites temperatures of 110° and 112° F. in such cases. As an illustration of how low the temperature may run, the following temperature record of a fatal case of quotidian estivo-autumnal fever may prove interesting. This case was observed by the author, and the morning and evening temperatures only are given, as there was no rise during the intervening hours. The temperature record is as follows:

July 15, A. M., 98.4° F.; P. M., 101.° F.
July 16, A. M., 99° F.; P. M., 99.6° F.
July 17, A. M., 98° F.; P. M., 97.8° F.
July 18, A. M., 96.4° F.; P. M., 98.° F.
July 19, A. M., 100.2° F.; P. M., 98.° F.
July 20, A. M., 103.° F.; P. M., Died.

In this case the disease was not recognized by the attending physician until the 19th of July, when the blood was examined by the author and found to contain large numbers of quotidian estivo-autumnal parasites.

Auscultation of the lungs in the comatose form of pernicious malarial fever often demonstrates the presence of rales both at the apices and the base of the organs, and, not rarely, marked signs of extensive congestion. The right heart is generally, upon percussion, found dilated, and a systolic murmur is sometimes heard at the mitral valve.

One attack of comatose pernicious fever is apt, if untreated, to be followed by another, and this by another, and any of these attacks may prove fatal. The disease may prove fatal even after quinine has been properly administered, and even though it has been administered during a preceding comatose paroxysm.

The number of parasites found in the peripheral blood is not always a criterion as to the perniciousness, as one of the most rapidly fatal cases I have ever observed showed but few parasites in the peripheral blood. The capillaries of the brain in this case, however, showed multitudes of the parasites.

The symptoms in the comatose form of pernicious estivo-autumnal malarial fever are probably as much due to poisonous materials elaborated by the parasites as by their special localization in the cerebrum.

OTHER CEREBRAL PERNICIOUS FORMS OF ESTIVO-AUTUMNAL MALARIAL FEVERS

Besides the comatose form of pernicious malaria are several other forms in which the cerebral symptoms predominate. Among them may be mentioned the *delirious* form, in which the patient has hallucinations, followed by violent excitement; the *tetanic* form, characterized by trismus, convulsions, opisthotonos, and delirium; the *eclamptic* form, especially common in

children, which is very similar in symptomatology to cerebro-spinal meningitis, there being vomiting, fever, headache, pain in the back of the neck, with stiffness, convulsions, and coma; the *hemiplegic* form, characterized by hemiplegia, associated with coma; the *amaurotic* form, in which the comatose symptoms are followed by complete blindness, which may be very persistent. Blindness may also occur during the attack.

The attacks associated with symptoms of *bulbar paralysis* are very interesting, and have been studied by Marchiafava, Bignami, and Bastianelli, chiefly. Marchiafava thus graphically describes the symptomatology of this form of the disease: "The chief symptoms are difficulty in articulation, which may even reach anarthria, a weak and nasal voice, inferior facial paralysis often of one side only, a half-open mouth from which drops the saliva, a pendent lower lip, a dry and only slightly movable tongue, difficult or abolished deglutition. With these symptoms there are sometimes associated disturbances of equilibrium which recall the staggering gait of cerebellar disease. In a case of relapse Bastianelli and Bignami noticed an unsteadiness of gait as in drunkenness, diminution of strength of the left side, right facial paralysis, deviation of the tongue to the left, difficulty in speaking, nasal voice, grave prostration, and apathy."

The symptoms in these cases, under proper treatment, do not persist for a longer period than two weeks, as a general rule. The *ataxic* form of pernicious malaria has been carefully studied by Angelini and Torti, but it is very rare.

The Algid Form.—In certain localities the form of pernicious estivo-autumnal fever about to be described is not uncommon. In some of our southern and middle states the algid form is to be observed and is described under a variety of local names. The algid symptoms may develop after one or more paroxysms or they may be the primary symptoms.

The characteristic condition is one of collapse, generally very great, attended by profuse perspiration, the temperature at the same time being more or less elevated; in some cases the temperature is subnormal.

The face of the patient is characteristic, being drawn and pinched, the eyes sunken and often the typical Hippocratic facies is seen. The skin of the entire body is cold and cyanotic in color, and bathed with a cold sweat; the lips and finger-nails are intensely cyanotic; the tongue is very tremulous, and generally dry

and coated with a peculiar dirty white fur; the pulse is rapid, thready, and easily compressible, and generally more or less intermittent; the heart-sounds are muffled and the second sound sometimes inaudible; very often the pulse is imperceptible; the respirations are labored and irregular, being rather superficial in character, gradually becoming weaker and weaker as death approaches; the muscular weakness is extreme, the slightest movement being often impossible without great effort; the mental condition of the patient is one of apathy to his surroundings and indifference as to the gravity of his condition; the voice is weak and often almost inaudible. The algid symptoms rarely last over a few hours and are generally followed by death. No form of pernicious malarial fever is less amenable to treatment than is this form, and despite the most earnest therapeutic measures, a fatal termination is generally the rule, rather than the exception. Sternberg, Laveran, Thayer, Marchiafava and Bignami have described very typical cases of this form of the disease. I remember one very marked case in the person of a volunteer soldier who contracted estivo-autumnal fever in Cuba. He had several previous paroxysms, none of which showed any great severity, but during the last paroxysm algid symptoms developed and death occurred after six hours, despite all therapeutic aid. His blood showed large numbers of the unpigmented and pigmented tertian estivo-autumnal parasites.

The Choleraic Form. — Certain cases of pernicious estivo-autumnal malaria present symptoms very closely simulating those of cholera. Marchiafava has studied very accurately a number of such cases, and other writers have also observed them. It is not rare to have more or less diarrhœa present during estivo-autumnal attacks, but in cases presenting the choleraic symptoms, the stools suddenly become watery, very profuse, and numerous; they may be blood- or bile-stained, and contain mucus in the form of small flakes; the profuse diarrhœa leads to collapse, the face becoming pinched, the eyes sunken, the skin more or less cyanotic; a cold, clammy perspiration covers the skin, the pulse and respiration become greatly weakened; the patient, in a husky or tremulous voice, complains of severe cramps in the abdomen and thighs, and great thirst; he is greatly worried over his condition, and there is great mental depression. Death is the usual result in untreated cases, but where proper therapeutic measures are employed, the majority of the cases will recover. The tem-

perature in the choleraic form is generally elevated. It is rarely that a recurrence of the choleraic symptoms takes place, but when it does the result is almost invariably fatal.

This form of pernicious estivo-autumnal malaria simulates cholera so closely that the differentiation is very difficult, especially in countries where epidemics of cholera are common. The microscopical examination of the blood is the only absolutely correct method of arriving at a diagnosis in such cases and should never be neglected, as the parasites, if the case be malarial, are always present in the blood in sufficient number to be found with the exercise of a little patience and perseverance. Nowhere is the microscope more useful than in the diagnosis of the pernicious forms of estivo-autumnal fever.

The Cardialgic Form.—This form of pernicious malarial fever is comparatively rare, and is generally associated in classification with the *gastralgic form*. The prominent symptoms are severe, agonizing pain in the epigastrium, accompanied by exhausting vomiting of matter tinged with blood. Hiccough is often a very distressing symptom, and severe hematemesis may occur. These symptoms occur, as a rule, during the febrile stage.

The patient presents an anxious expression of countenance, a dry, glazed tongue, brilliant eyes, the conjunctivæ markedly congested, a retracted abdomen, cold extremities, hurried respirations, and a rapid, weak pulse; he suffers intense pain, and either groans or calls out under the torture which he is enduring. In fatal cases collapse occurs, accompanied by the symptoms described under the *algid form*.

Laveran, Colin, and Haspel have described cases of the *cardialgic* and *gastralgic* form of pernicious estivo-autumnal fever. I have seen but one case conforming to this type. The patient was a soldier, twenty-two years of age, who had suffered repeatedly from malarial paroxysms in the Philippine Islands. During the last paroxysm he had most intense pain over the left nipple and the epigastrium, which radiated to the vertebral column and down the thigh; the pain was so intense that screams were forced from him. He vomited repeatedly blood-stained fluid and suffered greatly from hiccough. His temperature reached 103.4° F., his pulse was very rapid and thready, his extremities cold, and he complained of great prostration and was very anxious regarding his condition. Under repeated hypodermics of

quinine his condition gradually improved and he eventually recovered.

The Dysenteric Form.—Certain cases of estivo-autumnal fever present the characteristic symptoms of dysentery, i. e., frequent mucoid and bloody stools, tenesmus, colicky pain in the abdomen, progressive emaciation, fever, etc. I am satisfied that a considerable proportion of dysenteric cases occurring in tropical countries are due to malarial infection. I am convinced of this because of the results of blood-examinations of soldiers returning from the tropics. In the routine examination of the blood of all cases admitted to the U. S. General Hospital at the Presidio, California, as well as elsewhere, a comparatively large number of cases diagnosed as dysentery show malarial parasites in the blood, although no marked typical malarial symptoms are present. The prompt treatment by quinine resulted almost invariably in the disappearance of the dysenteric symptoms and a return to health. From my laboratory records I find that 65 per cent of the cases of unrecognized malarial fever were diagnosed either as chronic diarrhoea or dysentery. This proves how commonly dysenteric symptoms in the tropics are due to malarial infection, and how important a microscopical examination of the blood is in all cases of dysentery occurring in tropical and sub-tropical climates.

The Diaphoretic Form.—This form of pernicious estivo-autumnal fever is characterized by the occurrence of very profuse sweating, so severe as to produce collapse and even death. This form of the disease is comparatively rare.

The Hemorrhagic Form.—Marchiafava and Laveran have described cases of pernicious malarial fever characterized by severe hemorrhages into the skin and mucous membranes, as well as the occurrence of hematomesis, epistaxis and hemoptysis. These symptoms may be so severe as to cause collapse and death. The temperature is extreme in most of this class of cases. This form of the disease is undoubtedly very rare, and I have never observed such a case. Epistaxis, even of quite severe character, is not, however, a very rare symptom in attacks of estivo-autumnal malarial fever. I have observed a large number of cases which presented epistaxis during the paroxysms of a malarial infection.

The Pneumonic Type.—To Baccelli we owe the demonstration of a class of estivo-autumnal fevers of pernicious character, which, in their symptomatology, simulate pneumonia. The chief

symptoms are cough, pain in the side, dyspnoea and the expectoration of blood-stained sputa. Percussion shows dullness over the affected lung, and auscultation coarse, sibilant rales. The condition is not a true pneumonia, but is due to congestion brought about by the stoppage of the lung-capillaries by the parasites and their products. I am indebted to Major Charles Richard, surgeon of the United States army, for the following interesting example of this form of estivo-autumnal fever:

"The patient, a soldier, gave no history of a previous malarial attack. He had suffered for some days from fever, but had no chills. Had much pain in the chest, a cough with expectoration, and some vomiting. The maximum temperature was 104° F., but there was no regularity in the curve. The man looked very sick and was the picture of acute lobar pneumonia. Physical examination showed a general bronchitis. The spleen could be felt below the ribs. The examination of the blood showed numerous "ring-forms" of the estivo-autumnal parasites, and treatment with quinine resulted in recovery."

The Bilious Form ("Subcontinua bilosa").—There are certain cases of pernicious estivo-autumnal malaria which present a complex of symptoms in which jaundice and the vomiting of bile-stained fluid are most prominent. These cases are usually attended by a more or less continuous fever, which may be greatly above normal. The attack is generally characterized in the beginning by a tertian or quotidian paroxysm, most frequently a tertian, but the temperature soon becomes remittent or almost continuous. The skin is markedly jaundiced, the fæces deeply colored by bile, and the urine of a deep brown or even green color. Epistaxis is rather common, and hematemesis often occurs. The patient is either apathetic and hard to rouse or is delirious. Vomiting is often frequent and severe, and epigastric pain and hiccough is present. If untreated this form of the disease is usually fatal. If the proper therapeutic measures are instituted, recovery is generally the result, although cases occur which prove fatal despite all therapeutic efforts.

Of the very rare forms of pernicious malarial fevers may be mentioned the *syncopal* form, noted by Sternberg, characterized by attacks of syncope upon exertion during the sweating stage or period of deferrescence of the fever; the *exanthematous* form, characterized by the occurrence of a scarlatinaform rash upon the skin during the paroxysms, followed by desquamation; and the

pleuritic form, characterized by intermittent attacks of sharp pain in the side, a dry cough, and, on auscultation, friction sounds.

EXAMINATION OF THE BLOOD IN THE PERNICIOUS FORMS OF ESTIVO-AUTUMNAL MALARIA

The examination of the blood during an attack of pernicious malarial fever will almost invariably result in the demonstration of large numbers of the estivo-autumnal parasites. In no form of malarial fever are the parasites so numerous in the peripheral blood as they are in the pernicious estivo-autumnal fevers. Often a single field will contain from ten to twenty infected corpuscles.

The findings in the blood vary somewhat, according to the period of time in which the examination is made, and according to the type of fever present.

In a case of regularly intermittent pernicious estivo-autumnal fever, if the blood be examined at the acme of the paroxysm, the parasites present will be mostly of the unpigmented variety, while if the blood be examined during the intermission or one or two hours before the beginning of the paroxysm, the pigmented forms of the estivo-autumnal parasite will be found. At whatever time the blood is examined, however, it will be found that the parasites are all approximately in the same stage of development.

On the other hand, if the blood of cases suffering from pernicious estivo-autumnal fever, in which the temperature curve is irregular, or almost continuous, be examined, it will be found that both unpigmented and pigmented parasites will be present, at whatever period the blood be examined.

A few words in regard to the importance of the examination of the blood in all cases residing in or coming from malarious regions, whenever there is a shadow of a doubt regarding the disease present: As has been shown, the pernicious malarial fevers present themselves in so many disguises, and exhibit so often so many atypical symptoms, that even the most acute clinical diagnostician may be entirely deceived regarding these cases. The one scientific and entirely satisfactory way of diagnosing any form of malarial fever is by the microscopical examination of the blood; it consumes but little time, is absolutely conclusive in its results, and, better than all, it may save the life of the patient entrusted to the physician's care. It should never be neglected in regions in which the estivo-autumnal fevers are prevalent, as it is

in these fevers that its value is greatest. The fact should ever be held in mind that any estivo-autumnal fever may become pernicious, and that the longer it remains unrecognized and untreated the greater the chances of its becoming so, and the greater the danger to the patient. Ignorance of the use of the microscope is no excuse for an omission which may cost a human life.

In illustration of this I have in mind the case of a soldier, believed to be suffering from acute catarrhal jaundice. His symptoms, upon entering the hospital, were so typical of this condition that the physician in charge delayed the examination of the blood for several days. During this time the patient ran an irregular temperature, never above 101° F., became very much jaundiced and finally lapsed into a semi-comatose condition. At this time the blood was examined and was found to be literally loaded with quotidian estivo-autumnal parasites. The most energetic treatment was at once instituted, but despite all that could be done the patient died in a few hours. Without doubt this man's life could have been saved had the blood been examined earlier, before the intense malarial intoxication had occurred. It is in such cases as this that the microscope becomes a life-saving agent more powerful than the surgeon's knife or the therapist's art.

CHAPTER XV

LATENT AND MASKED ESTIVO-AUTUMNAL MALARIAL FEVERS— SUBCONTINUED ESTIVO-AUTUMNAL MALARIAL FEVERS—COM- BINED INFECTIONS.

LATENT AND MASKED FEVERS.—The subject of latent and masked forms of the estivo-autumnal malarial fevers has not received the attention and study which it deserves. If such a thing could be possible as the microscopic examination of the blood in all cases of disease, in all parts of the world, it is safe to say that the number of cases proving to be due to the presence in the blood of the malarial parasites and diagnosed as other disease processes would be so astounding as to be almost unbelievable.

In latent and masked estivo-autumnal fevers we include all cases in which the estivo-autumnal parasites may be demonstrated in the blood, but in which either no clinical symptoms are present or the symptoms which are present are atypical in character.

A still closer definition of these terms may be made as follows:

a. Latent estivo-autumnal malarial fever, in which the parasites can be demonstrated in the blood, and no clinical symptoms of any disease are present.

b. Masked estivo-autumnal malarial fever, in which the parasites are present in the blood, but the symptoms present are those of another disease, or are atypical.

In the first-named class occur those cases discovered accidentally through an examination of the blood for some other purpose. Such cases have shown absolutely no symptom of malarial fever or other disease, yet numerous parasites may be found in the blood. I can recall a large number of cases in soldiers who have had their blood examined as a routine measure, in which the estivo-autumnal parasites were found, although there were no symptoms of the disease present.

As a rule, in such cases, the number of parasites is com-

paratively small, but there may be much free pigment present and numerous pigmented leucocytes. In blood from the spleen in these latent cases the entire human cycle of the estivo-autumnal parasites can be followed.

The tertian estivo-autumnal parasite is the most common form found in such cases, although the quotidian form is by no means rare. The only explanation of the fact that the development of the malarial parasite may not, for a considerable period of time, be accompanied by clinical symptoms is either that the parasites are present in too small numbers or that the individual infected is very resistant to the action of the malarial poison.

The length of time during which such a latent infection may exist is as yet undetermined, but it is probable that in some cases it may be for many weeks. I recall one case in which the estivo-autumnal parasites were found in the peripheral blood for six weeks before a paroxysm occurred, repeated blood-examinations being made during that time. I can recall many cases in which the parasites were found for from seven to fourteen days before clinical symptoms appeared.

The second or masked estivo-autumnal malarial fevers constitute a much larger class of cases, and their recognition is of the utmost importance from a practical point of view.

Such cases very often present no rise of temperature, and, in fact, the temperature is often subnormal. Nervous symptoms, such as slight headache, vertigo, neuralgias of various parts of the body, etc., or symptoms referable to some other disease may be present, as diarrhoea, acute or chronic dysentery, pneumonia, typhoid fever, etc.

It should always be borne in mind, in treating diseases in localities in which the estivo-autumnal parasites are prevalent, that some of the most pernicious forms of these fevers are unaccompanied by definite paroxysms or a rise of temperature, and that the temperature is not rarely subnormal. I recall a fatal case of quotidian estivo-autumnal fever in which the temperature never rose above 99° F., and in which the few symptoms present were those of an acute hepatitis. Examination of the blood, a few hours before death occurred, showed large numbers of quotidian estivo-autumnal parasites, and the findings at autopsy were typical of death from pernicious malarial fever.

I would it were possible to impress upon every practitioner

the absolute unreliability of clinical symptoms in many cases of estivo-autumnal malarial fever, so far as diagnosis goes, and the infinite importance of a microscopical examination of the blood in all cases of disease occurring in malarial regions.

As an illustration of this I will quote from the record of my examinations in the U. S. Army General Hospital at San Francisco, Cal. By order of Colonel Girard, the commanding officer, every case entering this hospital has a blood examination made, whether or no clinical symptoms of malaria are present. For a period of nine weeks fifty-six cases were found, none of which presented any symptoms of malarial fever, yet in which the peripheral blood contained the malarial parasite.

An analysis of these cases is of interest. Thirty-seven were infections with the estivo-autumnal parasites, while nineteen were infections with the benign tertian parasite. Of the infections with the estivo-autumnal parasites, twenty-four were infections with the tertian estivo-autumnal parasites and thirteen with the quotidian estivo-autumnal parasites.

The thirty-seven cases showing the estivo-autumnal parasites in the blood were diagnosed, from the clinical symptoms present, as follows: chronic dysentery, sixteen cases; chronic diarrhœa, five cases; chronic gastritis, one case; phthisis pulmonalis, five cases; bronchial asthma, one case; undiagnosed, nine cases.

From the above it will be seen how little faith can be placed in clinical symptoms in many of these cases, and how important an examination of the blood is in all cases of disease.

It may be said in passing that chronic diarrhœa or dysentery is very commonly associated with the malarial fevers in soldiers returning from the Philippine Islands, and a very marked improvement in the intestinal symptoms almost always follows the treatment of the malaria with quinine.

In many cases symptoms of a complicating disease will entirely mask those of estivo-autumnal fever, and only an examination of the blood reveal the malarial element in the case. This is especially true in cases complicated with pneumonia and typhoid fever.

SUBCONTINUED OR REMITTENT ESTIVO-AUTUMNAL MALARIAL FEVER.—Certain cases, both of tertian and quotidian estivo-autumnal fever, instead of presenting distinct paroxysms, separated by an intermission, run a more or less continuous or slightly remittent course. I have already discussed the various

ways in which an intermittent malarial fever may become continuous or remittent, but will briefly recapitulate here:

1. The paroxysms may be prolonged so that they overlap each other, thus causing a remittent temperature curve.

2. The paroxysms may anticipate, one beginning before the preceding one ends.

3. The paroxysms may be duplicated.

4. By a mixed infection of the quotidian and tertian estivo-autumnal parasites.

In these remittent or subcontinuous forms of the estivo-autumnal fevers, the generation of parasites causing the original attack is seldom to be demonstrated; but in mixed infections both forms of the parasites may usually be easily demonstrated in the blood. It is these forms of malarial fever which are so often mistaken for typhoid fever or septicemia, especially by practitioners in localities where the estivo-autumnal fevers are rare. These are the forms of malaria which were supposed by many surgeons during the war with Spain to be present in the southern camps, whereas, in reality, the cases so diagnosed were typhoid fever. If there is one thing in the medical history of this country which should teach the profession the folly of diagnosing the malarial fevers by the symptoms alone it is the experience of our armies in the camps throughout the South during 1898.

Symptoms.—It is but rarely that a case of remittent or subcontinuous estivo-autumnal fever is observed for a period of time sufficient to gain an adequate idea of its symptoms and course, as quinine is generally given at the beginning and the attack cut short. In cases, however, which have been studied, the symptoms have been found to be very variable and often inconstant. The prodromal symptoms are general weakness and malaise, headache, loss of appetite, etc. The attack usually begins without a chill, although there may be slight chilly sensations or "creepy feelings." The patient's appearance is often very suggestive of typhoid, the face being flushed, the eyes brilliant, the conjunctivæ inflamed, the skin hot and dry, the headache very severe, and general pains present in the back and limbs; the patient is often very nervous and restless, sleeping poorly and waking with a start, and there may be slight delirium. The tongue is dry and coated, nausea and vomiting are present, and diarrhœa is common; the pulse is rapid and dicrotic, the respirations hurried and often superficial, the abdomen often

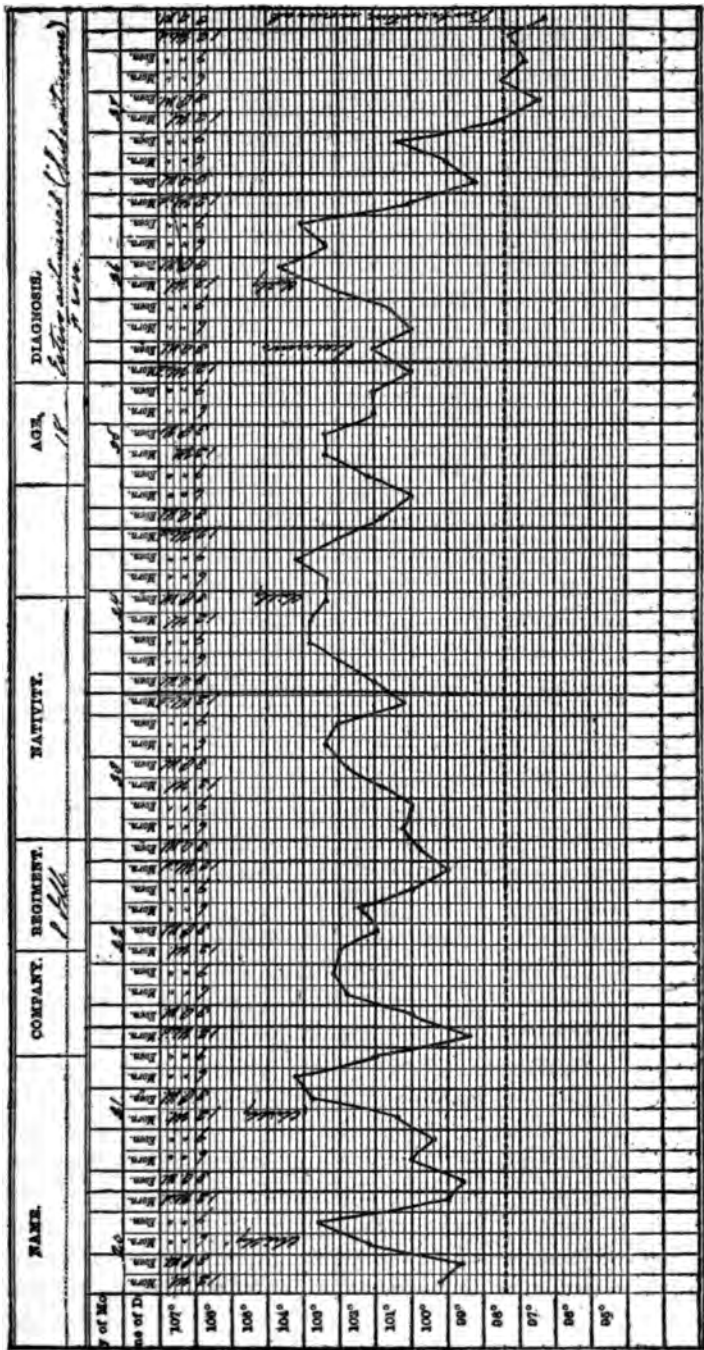


Chart No. 16. Subcontinued or Remittent Estivo-autumnal Fever.

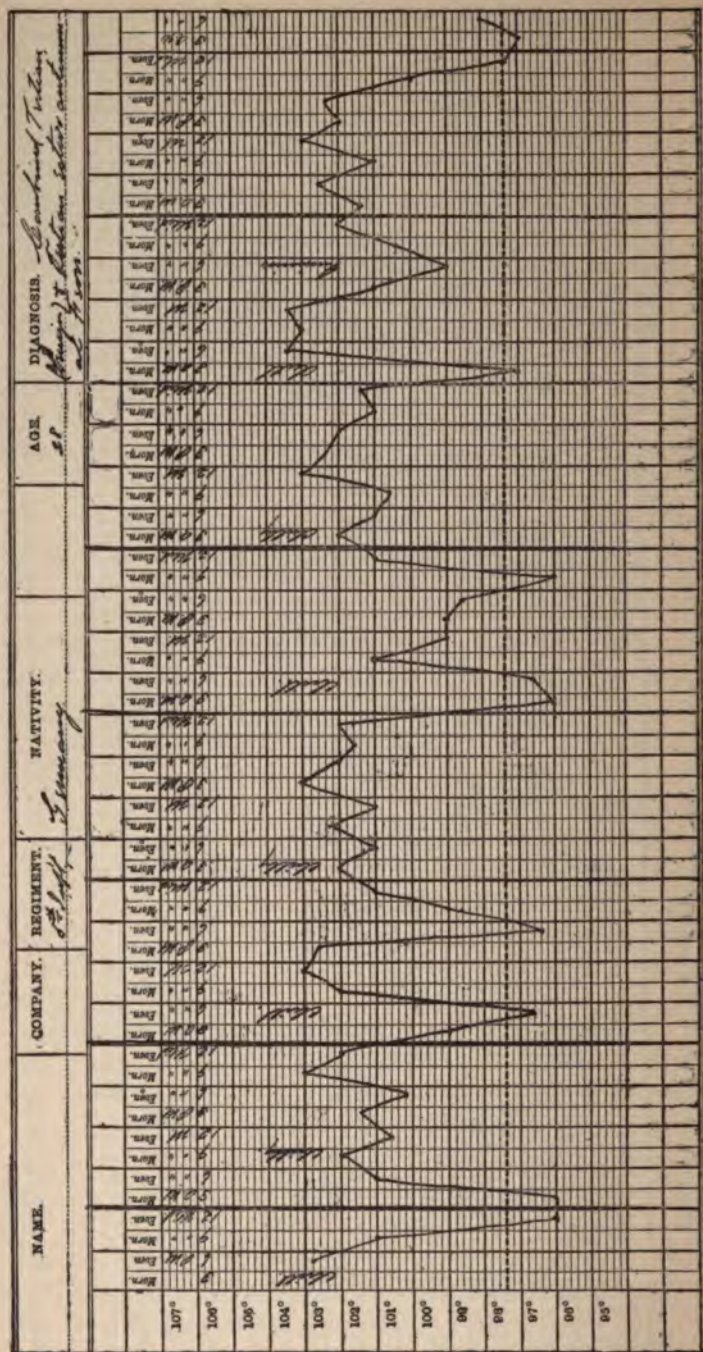


Chart No. 17. Combined Benign Tertian and Tertian Estivo-autumnal Malarial Fevers. The paroxysms occurred independently.

tender, and the spleen always more or less enlarged. In those cases which most closely simulate typhoid fever, the resemblance is indeed startling—epistaxis, roseolar eruption, gurgling and tenderness in the right iliac fossa, etc., all being present in addition to the symptoms already enumerated. Before the discovery of the malarial parasites such cases caused much confusion, but to-day an examination of the blood will demonstrate their nature immediately. It is to this class of cases that the term typho-malarial fever has been applied, but the microscope has definitely proven the falsity of this appellation. There is no doubt that typhoid and estivo-autumnal malarial fever may coexist, but there is no such disease entity as typho-malarial fever.

The temperature curve in the remittent estivo-autumnal malarial fevers is very variable, but there may usually be traced slight intermissions corresponding to the ending of the paroxysms. Sometimes, however, the curve much resembles that of typhoid fever, there being slight daily remissions; this is especially true of the subcontinued fevers due to the quotidian estivo-autumnal parasite. The chart shown is fairly typical of such a fever. (Chart No. 16.)

The examination of the blood in these fevers shows the same parasites which cause the more regular forms of estivo-autumnal fever. As a rule, the parasites are fairly numerous and are generally in various stages of development.

Besides the typhoidal types of remittent malarial fever, various other forms have been described, as the bilious, pneumonic, etc., but such a classification is loose and unscientific and undeserving of special consideration. The point to be remembered is that there occur many forms of estivo-autumnal malarial fever which pursue a more or less remittent or continuous course as regards temperature, and resemble clinically other febrile processes, and that the only way of quickly and satisfactorily diagnosing them is by the microscopical examination of the blood.

Duration of Remittent or Subcontinued Estivo-autumnal Fever.

—If untreated the fever may continue for several weeks; but, as a rule, spontaneous cure or death occurs within three weeks. These fevers are apt to become pernicious at any time and death may occur suddenly. If properly treated a cure is usually effected within a week, but some cases are very resistant to quinine, and may persist for eight or ten days.

COMBINED INFECTIONS.—The estivo-autumnal parasites may be

occur in the blood in conjunction with the tertian parasite, or with each other. In such cases the temperature chart is apt to be irregular. It is very often the tertian parasite may be associated in the blood with the estivo autumnal parasites without affecting the course of the temperature. If, however, the tertian parasites are present in sufficient numbers to affect the temperature, some very peculiar temperature curves may be produced. Chart No. 17 is a beautiful illustration of such a case, in which the estivo autumnal and the tertian parasites are associated independently of one another, as was shown both by the chart and the examination of the blood.

IMPORTANCE OF THE EXAMINATION OF THE BLOOD IN ALL LOCALITIES OF MALARIAL LOCALITIES.—I have already spoken of the importance of blood examinations in all malarial cases, but will still further to emphasize their importance in all diseases occurring in malarial localities and in all patients coming from such localities. I speak of this matter not from theoretical knowledge, but from practical experience. I can recall more than one instance in which a single blood examination saved a human life, in all probability, and it is because of such facts that I urge upon every practitioner of medicine the importance of the microscope in the practice of his profession. The malarial fevers are most infectious and most destructive diseases, and this is especially true of the estivo autumnal malarial fevers.

In the latent cases the examination of the blood is our only means of diagnosing the disease. Such an examination, if positive, enables us to combat the disease before the clinical symptoms have appeared, and thus saves the patient much discomfort and danger; in the masked cases the microscope, again, is our only hope, and a positive examination enables us to treat the malaria and sometimes save a life which might otherwise have been sacrificed. In the remittent and subcontinued forms the microscope and quinine are our diagnostic resources. Quinine is slow and not always sure; the microscope is quick and absolutely reliable, and a positive examination enables us to diagnose the disease from typhoid fever and apply the proper treatment. Had every surgeon during the Spanish war owned a microscope, and known how to use it, hundreds of lives would have been saved; the great typhoid epidemics would have been, in large part, prevented, and health and life would have reigned

instead of disease and death. This is not a flowery pen picture, but the statement of actual fact, for if the first cases of typhoid had been recognized and the proper precautions taken, there would have been no great epidemics such as devastated nearly all our southern camps. A clear understanding of the nature of the estivo-autumnal malarial fevers, together with a knowledge of microscopy sufficient for the recognition of the parasites causing such fevers, should form part of the armamentarium of every physician.

NOTE.—Since writing the section upon latent and masked estivo-autumnal fever, I have kept a record of the cases in which malarial parasites were present in the blood, but the diagnosis other than malaria, and have, in nine months, at the United States Army General Hospital at San Francisco, found one hundred and seventy-two such cases. These may be divided as follows: Tertian infections, thirty-six; quartan infections, one; estivo-autumnal infections, one hundred and thirty-one. Of the one hundred and thirty-one estivo-autumnal infections, one hundred and two were due to the tertian estivo-autumnal parasite and twenty-nine to the quotidian parasite. Forty-three of these cases were diagnosed as chronic dysentery, fifteen as chronic diarrhoea, in thirty-four no diagnosis was recorded, while the remaining thirty-nine cases were variously diagnosed. In none of these cases were typical symptoms of malarial fever present and it was only by the examination of the blood that it was possible to diagnose the condition. From this large number of cases it will be seen how important an examination of the blood is in all cases of disease.

CHAPTER XVI

COMPLICATIONS AND SEQUELÆ

COMPLICATIONS

LIKE all other acute disease processes, the estivo-autumnal malarial fevers may be complicated by, or associated with, other diseases; but the old idea, first advocated by Boudin, that these complications were due to the malarial poison, has long since been abandoned. The malarial parasites are not the cause of a pneumonia accompanying malarial fever, nor of a typhoid which may be coexistent with it; in each case the complicating disease is due to its specific organism, and though the course of either disease may be more or less affected by their association, yet its etiology remains unchanged. In other words, there is no such thing as a peculiar form of pneumonia or typhoid due to the estivo-autumnal parasites.

I shall classify the diseases which may complicate the estivo-autumnal malarial fevers under the following headings:

1. Diseases of the Nervous System.
2. Diseases of the Respiratory System.
3. Diseases of the Circulatory System.
4. Diseases of the Genito-urinary System.
5. Diseases of the Gastro-intestinal Tract.
6. Miscellaneous.

1. DISEASES OF THE NERVOUS SYSTEM.—Coincident with the estivo-autumnal fevers there may occur attacks of *acute mania*, and such cases have been described by Yanirris,* but this complication is very rare. *Hysteria* is not a very uncommon complication in nervous women or even in men, and, as in hysterical attacks in general, the symptoms complained of vary greatly in character and severity. *Paraplegia* and *hemiplegia* may rarely complicate these fevers, and neuroses of various kinds are not uncommon. *Meningitis* may also occur.

2. DISEASES OF THE RESPIRATORY SYSTEM.—Both *lobar* and

*La. Med. Orient., 1898., II., 6.

lobular pneumonia occur as complications, the first being by no means a rare complication. Early observers held that the pneumonia accompanying malaria was directly due to malarial poison; but recent investigations have conclusively proven that the malarial parasites *per se* are unable to produce a true pneumonitis. The pneumonia complicating malaria will always be found, upon bacteriological examination, to be due to the *diplococcus pneumoniae*.

I have already described the form of pernicious estivo-autumnal fever in which the symptoms are chiefly referred to the lung and are identical with those of lobar pneumonia. The condition present in these cases is due to a localization of the parasites in the lung capillaries. Microscopical examination of the lung, in such cases, shows that the lesions present differ widely from those common to lobar pneumonia.

Pneumonia may complicate the malarial infection at any time, and may develop suddenly or insidiously. The course of the pneumonia is generally but little altered, although the disease is apt to assume a more severe type than when it occurs alone. Pneumonic symptoms may entirely mask the malaria, or, on the other hand, may be so slight as to be masked by the malarial infection.

The *prognosis* in pneumonia complicating estivo-autumnal malaria is always very grave, many cases proving fatal. The mortality is stated by Ascoli to be as high as 60 to 78 per cent in patients who have had repeated estivo-autumnal attacks. Death may occur from thirty-six to seventy-two hours from the initiation of the attack.

In cases which recover, the convalescence is very slow, resolution being greatly delayed. An empyema may result in rare instances. Not rarely the affected portions of the lung become fibroid, and a *chronic fibroid pneumonia* results, or a *bronchiectasis* appears.

Pneumonia septicemia as complicating malaria, has been described by Bignami, Marchiafava, and Nazari.

Acute bronchitis is a very common complication of the estivo-autumnal malarial fevers, being observed in about 40 per cent of the cases. It may be very persistent and often very markedly weakens and exhausts the patient.

Tuberculosis.—The old belief that tuberculosis and malaria could not exist to any extent together has been exploded. We now know that both diseases are very commonly associated, and

that even fatal cases of estivo-autumnal malaria may occur in patients suffering from active tuberculosis. Marchiafava and Bignami have reported a very interesting case of this kind. Marchiafava claims that "if the malarial infection attacks organisms affected by tuberculosis, the latter is not arrested, but acquires a tendency to spread, and produces miliary tuberculosis." The same authority states that "according to our experience, malarial cachexia does not predispose to tuberculosis, as do other cachexias."

Pleurisy is a somewhat rare complication, and when it occurs pursues the same clinical course as is usual.

If quinine be administered to a patient suffering from any of the complications mentioned it will be followed by the cessation of the malarial symptoms, and the complicating process will run its usual course.

The diagnosis of estivo-autumnal malaria, when its symptoms are masked by complications, is only to be made by the microscopical examination of the blood.

3. DISEASES OF THE CIRCULATORY SYSTEM.—Any of the *organic* diseases of the heart which may be present at the time of an estivo-autumnal infection will complicate it, and often in such cases the prognosis is exceedingly grave.

Acute endocarditis may occur as a complication and the *ulcerative* form of the disease may follow a pneumonic complication.

Functional disorders of the heart are very common complications of the estivo-autumnal malarial fevers. A slow pulse during convalescence is common, sometimes counting but forty to the minute.

4. DISEASES OF THE GENITO-URINARY SYSTEM.—*Nephritis* is one of the most common complications of these fevers, and occurs in about 3 per cent of the cases. As a rule, the nephritis is an acute one, and generally subsides shortly after the cessation of the malarial attack. As nephritis is as much a consequence of malarial infection as it is a complication, I have considered it more fully in that portion of this chapter treating of the sequelæ of the estivo-autumnal fevers.

Orchitis and *epididymitis* not so very rarely occur as complications, but a history of gonorrhea is usually to be obtained. Some authorities have claimed that there is an orchitis due to the malarial poison, i.e., a malarial orchitis. I have never observed a case of this kind, although I have seen several cases of orchitis

complicating malaria, but there was invariably a venereal history obtainable. Personally I do not believe that a malarial orchitis or epididymitis ever occurs.

5. DISEASES OF THE GASTRO-INTESTINAL TRACT.—Various disorders of the gastro-intestinal tract may complicate the estivo-autumnal fevers. But I shall consider only two—dysentery and typhoid fever. *Acute* and *chronic gastritis* and *enteritis* are very common complications, and, during epidemics, *cholera* has occurred coincidently with malaria.

Dysentery.—In patients from certain localities dysentery is a very frequent complication of the estivo-autumnal infections. In the case of soldiers returning from the Philippine Islands, as observed at the U. S. General Hospital, at San Francisco, 65 per cent showing the estivo-autumnal parasites in the blood were also suffering from acute or chronic dysentery. Of this percentage, about 10 per cent were suffering from amoebic dysentery, as evidenced by the finding of the amoeba coli in the fæces. Dysentery complicating malaria, as I have observed it, runs an aggravated course, and is more apt to be fatal than when it occurs alone. Not infrequently the malarial infection appears to be latent, the dysenteric symptoms only being present. In Chapter XX, I have considered the diagnosis of such cases, but would repeat here that the blood of every case of dysentery coming from a malarial locality should be carefully examined for the malarial parasites. The administration of quinine in cases of estivo-autumnal malaria complicated by dysentery not only removes the malarial infection, but, in many instances, the dysentery improves and a return to health is more rapid. The explanation of this fact is not hard to find. We know from pathological study that the mucous membrane of the large intestine, as well as the small, is generally invaded by the malarial parasites, which invasion must necessarily injure the vitality of the tissues. Removal of the parasites by quinine obviously aids the tissues in regaining their normal condition and thus indirectly improves the dysenteric disease.

Typhoid Fever.—The simultaneous occurrence of typhoid and malarial fevers is a subject of much interest to investigators, one which has given rise to much controversy, and has evoked many varying opinions from eminent authorities. The only cases in which we can say that such a combination exists are those in which the plasmodia of malaria can be demonstrated in the blood and, at the same time, some substantial proof of the existence of

typhoid, as the separation of the bacilli from the excreta or a positive reaction to the Widal test, can be shown to exist. Such recorded cases are markedly few in number, if we consider the large number of cases in which the diagnosis of typho-malarial fever is made. In a recent publication, Dr. Irving Phillips Lyon* has collected all the published cases of combined typhoid fever and malaria on record, which have been proved to be such by the tests mentioned. These numbered only twenty-nine in all, most of them being cases of combined typhoid and tertian malarial fevers, and a few combined typhoid and estivo-autumnal fevers.

The old theory, announced by Woodward, that the conjunction of these fevers produced a typical disease, which he called typho-malaria, has been abandoned, and we now know that even the combination of these diseases is very rare. I have only observed five instances of such combined fevers in over four thousand cases of fever in which the blood was examined microscopically. Of these five cases, four were combined infections of typhoid and the estivo-autumnal malarial fevers, while one was a combined infection of typhoid and quartan malarial fever. The latter case is, I believe, the only one on record in which the quartan parasite was demonstrated in the blood. As a rule, the malarial attacks occur during convalescence from typhoid; but they may occur during the acute stage, or even at the very beginning. The symptomatology of the typhoid in such cases is but little altered, and there is nothing at all characteristic about the combined infection.

In such cases the malaria is almost always of long standing, and the attacks complicating typhoid are generally relapses.

The two following cases of combined typhoid and estivo-autumnal malarial fevers are interesting and instructive. The first, reported by Bevans,† occurred at the U. S. A. General Hospital at San Francisco, Cal. The following is the clinical history of the case, as given by Acting Assistant Surgeon Bevans, together with my report upon the examination of the blood:

"Corporal R. M., Co. K, 29th U. S. V. Inf., aged 21, born in Tennessee, was admitted on October 3, 1899. The man lived in his native state until enlistment in the Fourth Tennessee Volunteer Infantry in the fall of 1898. He then served in Cuba, and during his first service had a few light chills, which continued after his return home and until his reenlistment in August,

*"Am. Journal of the Medical Sciences," January, 1899.

†"New York Medical Journal," February 10, 1900.

1899. At this time he was apparently well. The chills appeared again at Fort McPherson, where he stayed about a month, and continued irregularly up to the time of his present sickness. En route to the Presidio, where he arrived October 1, he was confined to his bed with headache, constipation, general malaise and light chills. He had not, previous to that time, been on sick report. After three days in quarters in camp he was sent to the General Hospital. As he was brought into the ward he looked pale, emaciated and cold. His temperature was 102.4 ° F., respiration 22, and pulse 94. His tongue was coated, the abdomen tender, the liver and spleen were somewhat enlarged. His mental condition was dazed. By October 7 rose spots had developed, and he was in an active delirium. He had involuntary passages of urine and fæces. Light chills occurred daily after the 6th. On the 11th the chill was prolonged and severe. Malarial parasites were first found in the blood on that day. Quinine was then administered in large doses, and the last chill was observed two days later. Delirium continued until the 25th. The temperature curve and symptoms after the 13th were those of typhoid fever. The temperature reached normal on the 29th and slow convalescence has taken place.

"Examination of the blood: October 4. Examination for the plasmodia of malaria, negative. There are some leucocytes containing pigment. Widal test, negative.

"October 8. Malaria, negative.

"October 11. Numerous ring-forms of the quotidian estivo-autumnal parasite present. These are small, circular in form, somewhat refractive, the pigment consisting of from one to two small, almost black, specks. Not amœboid. The corpuscles containing the organisms are dark olive-green in color and shrunken. A few are crenated. Widal test, negative.

"October 13. Malaria, negative. Widal test, negative. There seems to be a slight clumping, but the bacilli remain motile.

"November 3. Malaria, negative. Widal test, negative. There are a very few minute clumps, but the bacilli remain motile. This may possibly be a very slight reaction, but I would ordinarily consider it as negative.

"November 9. Malaria, negative. Widal test, positive. Marked reaction immediately. It is interesting to note that this is the first positive reaction obtained, and raises the question as to whether or not the malarial complication hindered or lessened

the power of the blood to give a reaction. This may possibly be the explanation, although in the few cases of malaria complicating typhoid which I have seen, the Widal test has always been responded to promptly."

The history of the second case, observed at the Simpson U. S. A. General Hospital, Fortress Monroe, Va., is as follows:

"S. J., 8th Illinois, colored, arrived at Santiago, Cuba, upon August 16, 1898. Had suffered from chills and fever before leaving the United States, but does not think that he had malaria in Cuba, but suffered from diarrhoea and fever. Arrived at the Simpson Hospital on March 16, 1899, with a diagnosis of diarrhoea. Gave a history of having been sick for two weeks with diarrhoea and fever, but had had no chills. On the 17th he had a chill and his temperature rose. He suffered from headache, backache and nausea. Physical examination showed an enlarged spleen, tender abdomen, hot, dry skin and brilliant eyes. Heart and lungs normal. An examination was made of his blood, and numerous ring-forms of the tertian estivo-autumnal parasite were found, every field showing one or more. Quinine was at once administered, but as the temperature did not decline, the Widal test was made and a marked reaction obtained. All the typical symptoms of typhoid fever were present, and the course of the disease, after the malarial element was eliminated by quinine, was that of a gradually declining typhoid."

In this case it will be seen that the malarial complication occurred during the acute stage of the typhoid, as the patient had been suffering from the fever about two weeks before his entry to the hospital. A study of the chart (Chart No. 18) will show how little the malaria affected the course of the typhoid, and that but for the microscope a diagnosis could hardly have been reached.

The recognition of such cases as these is very essential, especially in treating fevers in tropical countries. The administration of quinine is proper in malarial fever, but in typhoid fever it is almost criminal, as grave mischief is often the result of such treatment.

Thayer* has very aptly discussed this point as follows: "The mere use of the term typho-malarial fever has indicated to many the advisability of the administration of quinine, and not infrequently this drug is used for days and for weeks in cases of uncomplicated typhoid fever in doses which cannot but be injurious to the patient. This is a matter of really grave importance.

*" Lectures on the Malarial Fevers."

It is one of the positions in which the physician actually has done and does do, to-day, really serious harm to his patient. There is no excuse for cinchonizing an individual with continuous fever who, after three or four days, shows no change in the symptoms, while the blood is free from malarial parasites."

In support of Thayer's statement, I may say that I have seen forty grains of quinine administered every day for four weeks in cases of simple typhoid fever which were supposed to be malarial in nature, and it is not too much to say that such treatment is criminal and cannot be too strongly condemned.

6. MISCELLANEOUS. — *Erysipelas* sometimes complicates the estivo-autumnal fevers, and in patients debilitated by prolonged malarial attacks is apt to be followed by *streptococcic septicemia*.

Insolation may complicate estivo-autumnal malaria and may aid in precipitating a pernicious attack. To Sternberg belongs the credit of first recognizing this complication, which is a most important one to guard against in the tropics. It is now generally admitted that an individual who has suffered from repeated attacks of malaria is much more sensitive to the sun's rays than one who has not, and that insolation is very apt to occur in such cases.

Acute rheumatism, sciatica, tonsillitis, parotitis, various skin eruptions, and *variola* have all been reported as complicating the estivo-autumnal malarial fevers.

SEQUELÆ OF THE ESTIVO-AUTUMNAL MALARIAL FEVERS

Properly speaking, the sequelæ of a disease are those affections which develop after the disease itself has ceased, but there are certain affections which arise during attacks of the estivo-autumnal fevers, which persist after the malarial symptoms have disappeared. These must be regarded as due to the effect of the malarial poison upon the system, and must, therefore, be regarded as sequelæ of the disease.

The various sequelæ may be divided as follows:

1. Diseases of the Nervous System.
2. Diseases of the Circulatory System.
3. Diseases of the Digestive System.
4. Diseases of the Genito-urinary System.
5. Diseases of the Glandular System.
6. Diseases of the Organs of Sense.

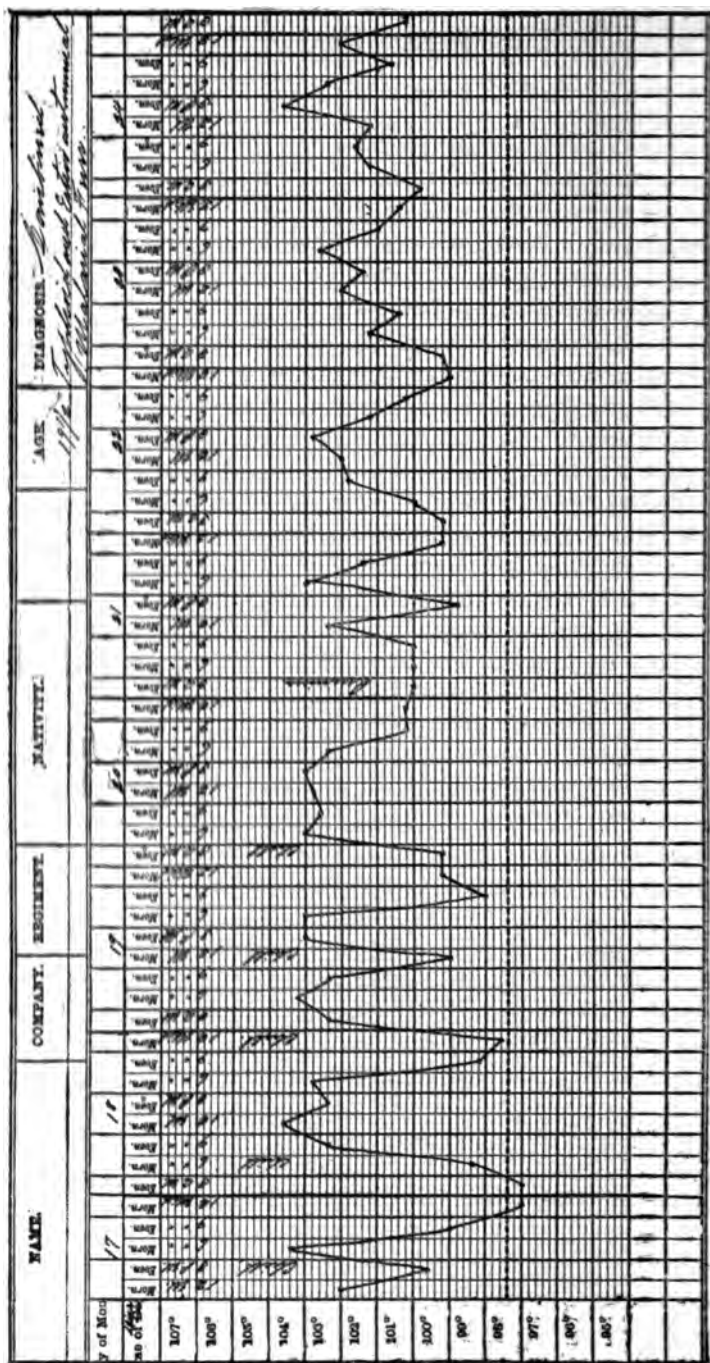


Chart No. 18.
Combined Typhoid and Tertian Estivo-autumnal Malarial Fevers (Plate A).

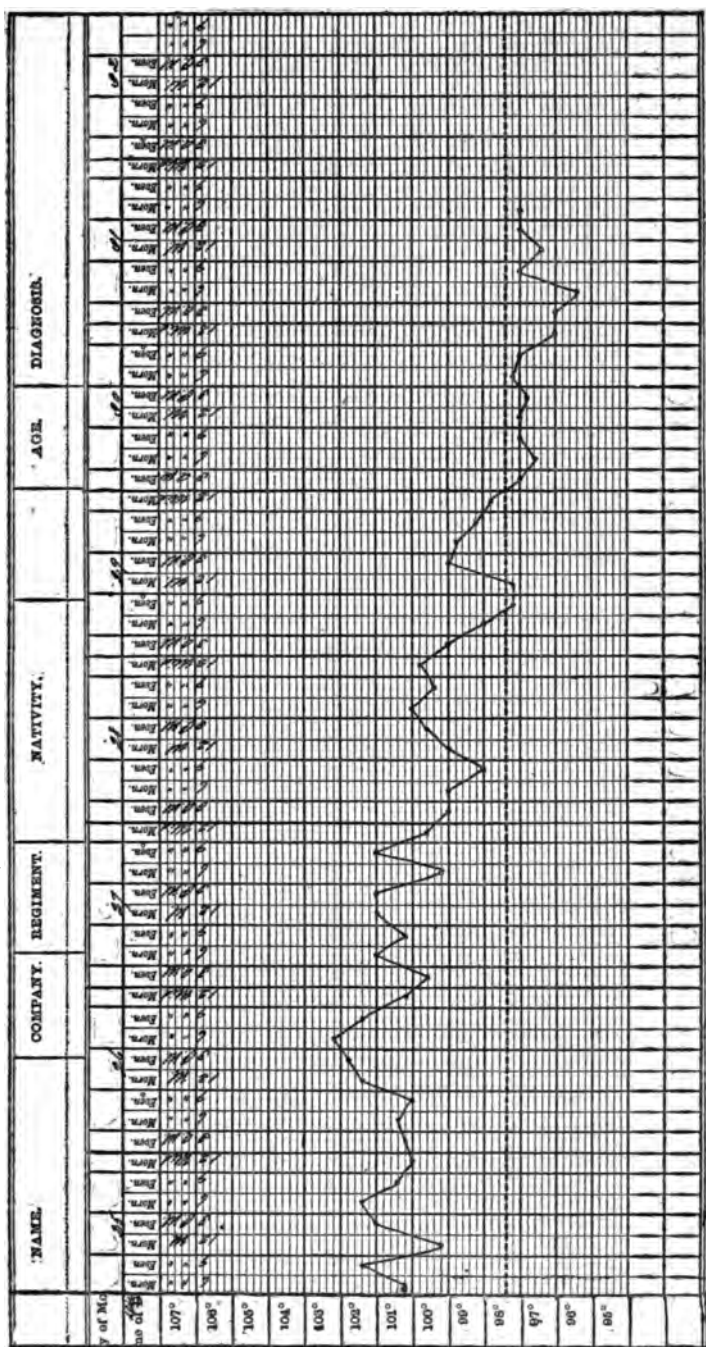


Chart No. 18.
Combined Typhoid and Tertian Estivo-autumnal Malarial Fevers (Plate B).

1. DISEASES OF THE NERVOUS SYSTEM.—The nervous affections which may occur with or follow the estivo-autumnal fevers are very numerous, and are especially common in the pernicious forms of the disease. The blocking of the capillaries of the cortex of the brain by the malarial parasites and free pigment often leads to evanescent *local paralyses*, which disappear under proper treatment. In some cases, however, they may remain for months. Such a case I recall in which a paresis of one side of the face developed during a severe estivo-autumnal attack, which persisted for two months after the fever was apparently cured.

Not uncommonly, after severe attacks, the mind seems to be unnaturally inactive, *memory* being defective, and sometimes an almost stuporous condition may be present.

Various *psychical* disturbances may occur, and *aphasia* is not very uncommon.

Melancholia, *mania*, and *delusional insanity* sometimes follow the estivo-autumnal malarial fevers. In some cases the mental depression occurring with and following the paroxysms is very noticeable, and it is a very common thing to have patients who have suffered from attacks of these fevers complain of having "the blues," or of ill-defined forebodings. An exaggeration of this condition becomes melancholia, which is not so very rare. I have observed cases of mania, melancholia, and delusional insanity in soldiers returning from the tropics, which were undoubtedly sequelæ of severe repeated attacks of the estivo-autumnal malarial fevers.

Multiple neuritis has been described as following estivo-autumnal malaria, by Gowers, Raymond and Jourdan. Glogner has studied very exhaustively several cases of *polyneuritis* following malarial fever, the symptoms consisting of severe pain in the lower extremities, increased by pressure, formication, partial or total weakness of sensibility, and response to electrical stimulation, weakness, and edema.

Chiarini and Bardellini have confirmed Glogner's observations and there can be no doubt that these cases of polyneuritis were due to malarial infection.

Bastianelli, Bignami, and Chiarini have described cases in which *electric chorea* or "Dubini's disease" was present in estivo-autumnal infections.

Neuralgia is a common sequelæ of estivo-autumnal malaria, although it should be noted that it is not as common as is gener-

ally supposed. Many cases of so-called malarial neuralgias have in reality no connection with malaria, and the name is used simply as a cloak for ignorance of the true etiology of the affection. The regions most affected by malarial neuralgia are the face and lumbar region. I recall a case of very severe sciatica following a tertian estivo-autumnal attack, which was finally overcome by quinine alone. The patient had never suffered from sciatica before and has never had an attack since.

2. DISEASES OF THE CIRCULATORY SYSTEM.—Lancereaux, Huchard, and a few other observers have endeavored to show that *endocarditis* and *arteritis* may be caused by malaria, but their arguments are illogical, and they furnish no convincing proof of the truth of their assertions. When these diseases occur with the estivo-autumnal fevers, they are complications and not sequelæ.

3. DISEASES OF THE DIGESTIVE SYSTEM.—As a result of the localization of the malarial parasites in the mucous membrane of the stomach and intestine, a true acute or chronic ulcerative enteritis and the formation of gastric ulcers may occur.

Pensuti, as quoted by Thayer, reports one case in which atrophy of the gastro-intestinal mucous membrane followed a malarial attack. From the results of a large number of autopsies performed upon patients dying of chronic dysentery, having suffered previously from malarial fever, I should be very much inclined to doubt the occurrence of such cases as that described by Pensuti, as even in these cases, which are certainly most liable to such changes, atrophy of the mucous membrane of the stomach and intestines, unless immediately around the dysenteric ulcers, is not common.

4. DISEASES OF THE GENITO-URINARY SYSTEM.—*Albuminuria* is of very common occurrence along with, and following, estivo-autumnal malaria. A large number of authorities have investigated this subject, and I will quote their results in brief. Thayer and Hewitson found it present in over 50 per cent of their cases. Regarding albuminuria Thayer* says: "Albuminuria was much more frequent in estivo-autumnal fever than in the regularly intermittent fevers, occurring in 38.6 per cent of the latter, and in 58.3 per cent of the former; while casts of the renal tubules were found in 12.2 per cent of tertian and quartan infections, and in 24.7 per cent of the cases of estivo-autumnal fever."

*"Progressive Medicine," March, 1899, p. 297.

Rem-Pici has contributed much to our knowledge of this subject, and he divides the albuminurias into the febrile, which occur with the paroxysms, or follow them at once, and the post-malarial, which occur after the malarial attack, and in malarial cachexia. From personal experience I believe that albuminuria occurs in about one-half of our cases of estivo-autumnal malarial, that it is most common in the tertian type of the disease, and that it is most common immediately after the paroxysm.

Nephritis.—Both *acute* and *chronic nephritis* may occur as sequelæ of estivo-autumnal malaria.

Kelsch and Kiener* have given the subject of malarial nephritis much study, and have described two forms of the disease, i.e., the glomerular nephritis and the granular nephritis.

The glomerular form is subdivided into acute and chronic, the first developing during or immediately after the acute malarial infection, the second during chronic infection. The clinical symptoms are those of acute and chronic parenchymatous nephritis.

The granular form is also divided into acute and chronic, the first developing in patients who have had numerous relapses of malaria, the clinical symptoms being those of subacute and chronic interstitial nephritis.

Rem-Pici divides the malarial nephrites into acute and chronic. The acute nephritis develops either during or after estivo-autumnal infections, and varies in severity and duration. As a rule, the prognosis is good for early recovery. He finds that it is most common in the autumn and winter, and in young, rather than old people. The most of these cases end in recovery, but a few become chronic.

The chronic form is a true interstitial nephritis, which may develop without a previous acute attack. At first it is a chronic parenchymatous nephritis, but later assumes an interstitial character. It is, however, much more rare than the acute form.

Amyloid degeneration may occur in the acute parenchymatous form of malarial nephritis.

From my own observations I should say that nephritis occurs in at least 3 per cent of the cases of estivo-autumnal malaria, and casts of the renal tubules are found in at least 25 per cent of the cases. Very rarely death occurs during the malarial attack as the result of an acute nephritis, but I have never observed such a case.

* "Políclinico," 1898, 197.

In Santiago, Cuba, during 1898, several such cases occurred among the American soldiers, and were at first regarded as cases of yellow fever.

Polyuria is not an uncommon sequelæ of the estivo-autumnal fevers. I have observed a large number of such cases, and in some instances the condition was very extreme. Polyuria is generally noticed just before and after the malarial attack. In one case, which was reported by Clark, the amount of urine passed during the twenty-four hours varied from 20,000 to 25,000 cubic centimeters for a period of several weeks.

Glycosuria was once thought to be a common sequelæ of this type of malaria, but later observations have shown that it is very rarely observed.

5. DISEASES OF THE GLANDULAR SYSTEM.—*The Liver*.—In cases which have suffered from repeated attacks of estivo-autumnal malaria, a condition known as hypertrophic malarial hepatitis develops, the organ being enlarged, sometimes enormously so, the perilobular tissue increased in amount, and the capillaries markedly dilated. This condition, however, does not cause marked disturbance in the functional activity of the organ, and no clinical symptoms are present which are characteristic.

Cirrhosis of the Liver.—Typical cirrhosis of the liver is, I believe, never the result of estivo-autumnal malaria. It may very rarely be present, but when it is, I believe it to be due to some other cause. That this is so, is evidenced by the fact that cirrhosis of the liver is no more common in malarial localities than it is in immune districts.

The Spleen.—In chronic malarial cachexia, due to the estivo-autumnal parasites, the spleen becomes often very greatly enlarged, and to this enlargement are due certain interesting sequelæ of the disease.

Floating Spleen.—In rare instances the enlarged spleen, by its weight, sinks into the abdominal cavity, the ligaments which hold it in place become stretched, and the organ can be felt as a movable mass through the abdominal walls. The symptoms produced are pain upon moving and reflexed disturbances, as headache, nausea, vomiting, etc.

Rupture of the Spleen.—The enlarged spleen is generally very soft and friable in acute infections, and very rarely this leads to rupture of the organ. This result may be induced by blows, falls, from retching in vomiting, or simply from sudden move-

ments of the body. The symptoms are sharp, lancinating pain in the left side, and the usual symptoms of collapse due to hemorrhage. Death may occur within a few moments, or a day, or even two, may pass before the fatal ending, depending entirely upon the amount of laceration present.

Abscess of the Spleen.—Laveran has described the formation of abscesses within the spleen, which he has termed malarial abscesses. Without doubt such abscesses have resulted from bacterial invasion, as the malarial parasite is not a pyogenic organism.

6. DISEASES OF THE ORGANS OF SPECIAL SENSE.—*The Eye.*—Affections of the eye are not very uncommon as sequelæ of the estivo-autumnal fevers, especially in the tropics. I shall describe briefly the most important.

Amiopia. In severe pernicious estivo-autumnal malaria, amiopia sometimes occurs, and is very often accompanied by other nervous symptoms. It is usually bilateral, and may last from a few moments to hours. In rare instances permanent blindness may result. It is most common with the tertian estivo-autumnal fever.

Purpurative Choroiditis.—A case of this kind which terminated in destruction of the eye has been described by Penhoff.

Iritis and Keratitis.—A few observers, notably Seluck, Van Milligen, and Kip have described cases in which iritis and keratitis have developed during estivo-autumnal attacks. Among the ocular changes which accompany chronic estivo-autumnal malaria may be mentioned optic neuritis, described by Sulzer; atrophy of the optic nerve, described by Bull; albuminuric retinitis described by Poncet, and effusion into the vitreous, described by Sulzer and Seely.

The Ear.—Certain affections of the ear have been ascribed to malaria, but only a few can be regarded as really due to malarial poison. These are: otalgia, intermittent in character, cases of which have been described by Frank, Politzer, and De Rossi; deafness, of intermittent character, described by Bar, Wolff, and Ferreri; labyrinthine vertigo, which has been well studied by Ferreri.

MISCELLANEOUS: POST-MALARIAL CHANGES IN THE BLOOD.—*The Anemia.*—In the estivo-autumnal forms of malaria, the anemia produced by repeated attacks may be very extreme and also very persistent. In the tertian and quartan fevers the

regeneration of the red blood-cells is very rapid as compared with the estivo-autumnal fevers, and in these the number of red corpuscles may reach a very low level. I remember several cases in which the number of red cells was but 900,000 per cubic millimeter, and one in which the blood-count showed but 497,000 per cubic millimeter. As a rule the greatest reduction occurs during the first paroxysms.

The *hemoglobin* is markedly reduced and always in about the same ratio as the red blood-corpuscles.

The *white cells* are reduced in number as a whole, but the large mononuclear forms are increased in number. A leucocytosis is generally an indication of the presence of some complication.

Pernicious Anemia.—The anemia following estivo-autumnal attacks is not always benign, but may gradually merge into a progressive and fatal form. Bignami, Bastianelli, and Dionisi have described two forms of pernicious anemia occurring after malarial fever.

1. A form, resembling in its clinical symptoms, blood findings and pathology, the classical type of pernicious anemia. In this form the blood shows poikilocytosis, the presence of microcytes, abnormally staining red corpuscles and nucleated red cells, chiefly megaloblasts.

2. The second form is most interesting, for while it is generally fatal, the blood does not show any nucleated red cells. This lack of nucleated red cells is due to the almost complete absence of regenerative power in the blood-forming organs, and the condition is similar to that found after profuse hemorrhage from any cause.

The latter form I have observed several times, the blood in the cases showing no nucleated red cells and the red cells numbering from 490,000 to 590,000 per cubic millimeter. The leucocytes were about normal in number, but the polymorphonuclear leucocytes were relatively increased in number. The blood in these cases showed but a very slight degree of poikilocytosis, but there were great differences in the size of the red cells.

Malarial Cachexia.—In persons who have suffered from repeated attacks of estivo-autumnal malaria which have not been properly treated, and who live in infected localities, a cachexia develops, which is the result of the malarial poison. This cachexia is, however, curable, and sometimes simply removal of the patient to an uninfected locality will result in recovery.

Patients suffering from malarial cachexia are very anemic; the skin is sallow; there is loss of appetite and energy, diarrhea, dyspnea, emaciation and many nervous disturbances. The liver and spleen are always enlarged, often enormously so. The temperature usually shows a slight rise toward evening, but seldom reaches 102° F. This condition is very common in children living in malarious localities, and, unfortunately, is often overlooked or diagnosed incorrectly.

Estivo-autumnal cachectics are very liable to acute infectious diseases, and slight injuries are apt to be followed by phlegmonous inflammation. Death, in the adult, rarely follows from the cachexia, but is the result of complicating processes.

Examination of the blood is very often unrewarded, but occasionally a ring-form of the parasite may be found, and crescents and ovoid bodies may be encountered in some cases. Pigmented leucocytes are more common, and a diagnosis can be made from them, provided the observer can recognize malarial pigment.

In closing this chapter I would call attention to the presence, in the tropics and in patients from the tropics, of estivo-autumnal malaria complicating wounds or surgical diseases. In such patients a rise of temperature during the treating of a wound or after operation, will, upon examination of the blood, be found to be due to malarial infection, and such an examination will often lift a load of anxiety from the surgeon and throw light upon obscure cases of fever.



CHAPTER XVII

THE DIAGNOSIS AND PROGNOSIS OF THE ESTIVO-AUTUMNAL FEVERS

DIAGNOSIS.—Unlike the tertian and quartan malarial fevers, the diagnosis of the estivo-autumnal fevers is often most difficult, and seldom easy. In making the diagnosis in this variety of malarial disease there are two methods which are alone deserving of confidence. These are the microscopical examination of the blood and the therapeutic test by quinine.

The examination of the blood is the most infallible method of arriving at a diagnosis and should never be neglected. The clinical symptoms in these cases are often so misleading, the periodicity of the attacks so often irregular, and the prognosis so grave, that to undertake a diagnosis by any other method is at once unsatisfactory and dangerous. The therapeutic test by quinine, while it is often decisive, should not be relied upon wholly, in these cases, as they are often very resistant to quinine, and thus the correct diagnosis of the case is long delayed, and the life of the patient endangered. There is but one absolutely reliable and scientific method of diagnosing the estivo-autumnal malarial fevers, and that is by the microscopical examination of the blood.

As a rule, one examination will be found sufficient; but if a negative result is obtained in a suspected case, repeated examinations should be made at intervals, for in many cases but few parasites are present in the peripheral blood, and these only at intervals. There undoubtedly occur cases of estivo-autumnal fever in which the parasites are so few in number in the peripheral blood that every microscopical examination may prove negative. From personal experience, I believe that such cases are very, very rare, and so mild in character that they are impossible to recognize clinically. I have never seen a case of acute estivo-autumnal infection severe enough to cause clinical symptoms which did not show parasites in the blood upon repeated examinations. On the other hand, I have records of

many cases in which but very slight or no clinical symptoms were present, yet parasites were found in the peripheral blood.

Among the factors to be considered in arriving at a suppositional diagnosis of estivo-autumnal fever, may be mentioned the time of occurrence of the disease, as in summer and autumn, in temperate climates; the locality, as to whether or not it is malarious; the location of the dwelling of the patient, and previous attacks; periodicity of the disease, etc.

DIAGNOSIS OF THE DIFFERENT TYPES OF ESTIVO-AUTUMNAL FEVER

The Quotidian Type.—The diagnosis of the quotidian type, when uncomplicated, is comparatively easily made, because of the presence, generally, of a distinct chill and the periodicity of the fever. The differential diagnosis of this type from that of a double benign tertian is impossible without the aid of the microscope.

The Tertian Type.—The diagnosis of the tertian type is much more difficult and often impossible clinically. The chill is, as a rule, either absent or very slight; the paroxysms are of long duration, and the general symptoms are so atypical in many instances that a diagnosis is very difficult. I have stated that the temperature chart, in an uncomplicated case of tertian estivo-autumnal fever, is absolutely diagnostic, provided the temperature be taken every four hours, at least, and this is so; but it would be folly to wait for several days in order to arrive at a diagnosis in this way when an examination of the blood, upon the very first day, will clear up the nature of the case at once.

In this form of estivo-autumnal malaria the diagnosis should rest chiefly upon the results of blood examinations.

The Pernicious Types.—In these types, so often resembling other forms of disease, a diagnosis in any other way than by a microscopical examination of the blood, is, as a rule, impossible. It is safe to say that hundreds of lives have been sacrificed to pernicious malarial fever which could have been saved had an examination of the blood been made. I can recall one case in which death followed pernicious attacks of malaria, in which the blood examination was delayed until too late for therapeutic measures to be taken, and several instances in which

death was narrowly averted by the discovery of the parasites in cases of unrecognized pernicious malaria.

In all cases in which a suspicion of malaria exists the first thought of the diagnostician should be the microscopical examination of the blood.

The Irregular and Continued Estivo-autumnal Fevers.—It is in this class of malarial cases that the microscope is of the greatest value to the practitioner. These cases, which present anomalous clinical symptoms, and irregular or continuous temperature curves, are very difficult of recognition and are often mistaken for other diseases. In many of them a diagnosis, from the clinical symptoms, is absolutely impossible, and it is in such that the microscope is of the greatest aid. A few moments' study of the blood will often demonstrate the nature of a case which has baffled the diagnostic acumen of eminent practitioners for days.

Upon what appearances in the blood can a diagnosis of estivo-autumnal malaria be made? First, and most important, upon the presence of the intracorpuseular, hyalin, or pigmented parasites. These are best looked for during the last stage of a paroxysm or in the interval. Often an examination of the blood at the beginning of a paroxysm will result negatively, but repeated examinations at intervals will generally demonstrate the parasites. Second, crescents and ovoid extracellular forms always denote an estivo-autumnal infection of some days' standing. Third, the presence of free pigment and pigmented leucocytes, provided a distinct history of chills cannot be obtained. If such a history is obtainable it is impossible to differentiate the type of malarial infection present from such appearances.

DIFFERENTIAL DIAGNOSIS.—The differential diagnosis of the estivo-autumnal malarial fevers from other disease processes, which may closely resemble them, is only possible, in many instances, by the use of the microscope. This is especially true of the typically intermittent quotidian type, which, by reason of its temperature curve, resembles many acute diseases. In the tertian type of estivo-autumnal fever the characteristic temperature curve, if present, is alone sufficient to differentiate it from other diseases; but in the pernicious and irregular cases the differentiation is most difficult without the aid of the microscope. I shall consider separately a number of diseases with which the estivo-autumnal fevers are liable to be confused.

Typhoid Fever.—There is no disease with which estivo-autumnal malaria has been so often confused as with typhoid fever. Our experience during the war with Spain is alone abundant proof of this assertion. At least three-fourths of the fevers occurring in the southern camps during 1898, and diagnosed as "remittent malarial fever," were, in reality, typhoid, as shown by the examination of the blood and the Widal test. Clinically, this confusion has often much to justify it. Many cases of untreated estivo-autumnal malaria present the same symptomatology, at least in part, as typhoid, and without an examination of the blood it is difficult to arrive at a diagnosis. The mistake of considering a typhoid infection as one of malaria, after quinine has been administered for over eight days without result, is, it seems to me, inexcusable, for all experience has shown that there is no malarial fever that will resist the action of quinine even after six days of its use; and yet hundreds of cases of typhoid fever are drenched with quinine, in supposedly malarial regions, under the mistaken notion that the estivo-autumnal fevers are so resistant to the drug that weeks of treatment are necessary. I have never seen a case of estivo-autumnal malaria which resisted the action of quinine for over six days, and doubt if any such exist, provided the quinine be properly administered.

The mistake of confusing an estivo-autumnal infection with one of typhoid is rather rare. In such cases the malarial attack may last for weeks and end in spontaneous recovery or death.

In differentiating these two diseases the microscopical examination of the blood, the Widal test, and the therapeutic test by quinine are to be relied upon. If the parasites are present in the blood and the Widal test is negative, the diagnosis is at once demonstrated, although rare instances occur in which the Widal test is not obtained in typhoid; they are so rare, however, as to be of no diagnostic importance. If a blood examination is impossible the use of quinine is indicated as a diagnostic measure. Any uncomplicated case of continued fever which resists the action of quinine properly given for a longer period than six days is not of malarial origin.

While the quinine test is valuable, it should be remembered that the microscopic examination of the blood is greatly to be preferred.

During the defervescence of the fever in typhoid, the tem-

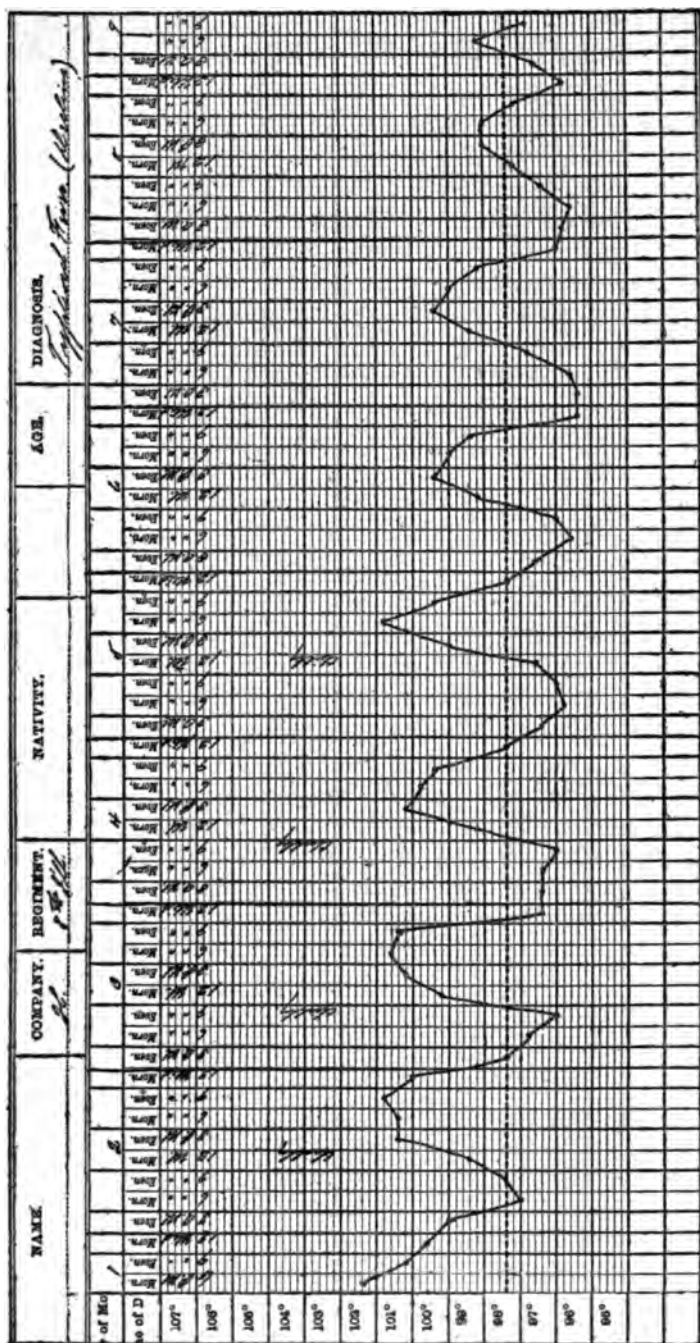


Chart No. 19. Typhoid Fever. Decline.

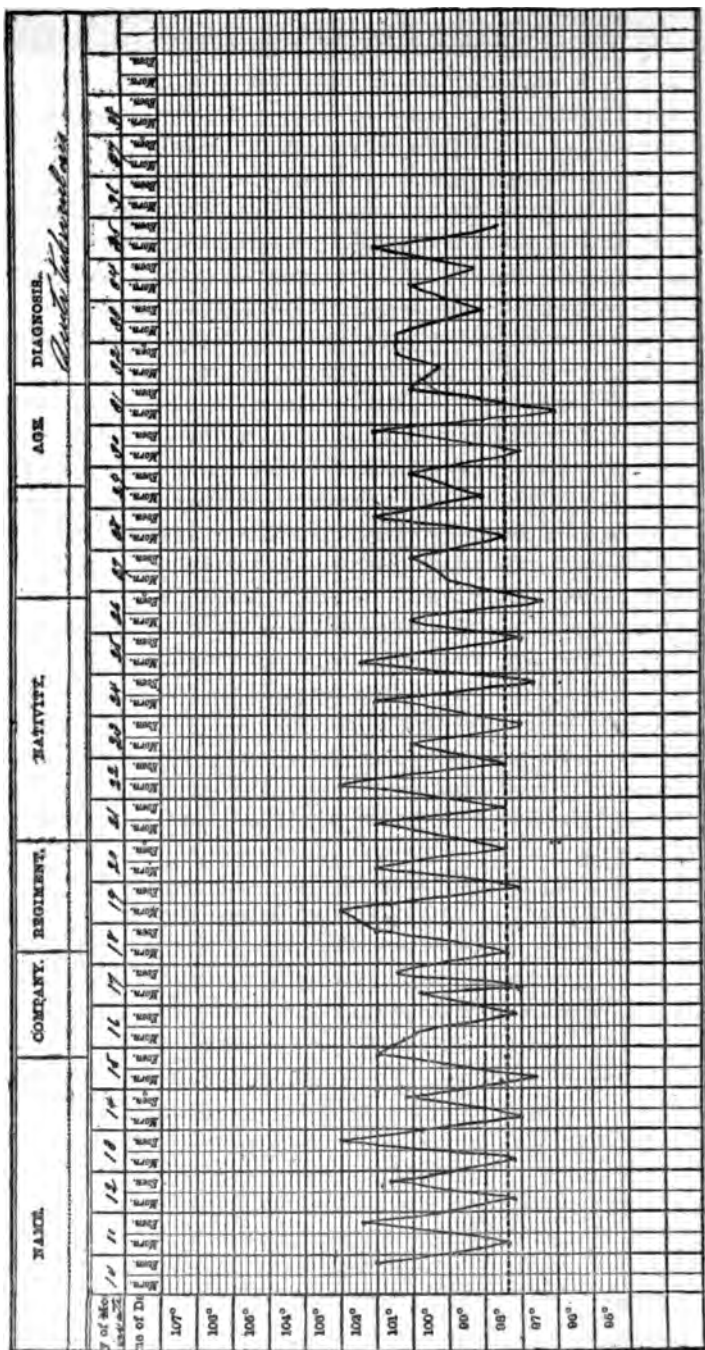


Chart No. 20. Acute Tuberculosis of Lungs.

perature may become intermittent, the curve much resembling that of a quotidian estivo-autumnal infection (Chart No. 19). Chills may also occur at this time, due to some septic complication, thus further increasing the resemblance, and a diagnosis is made of typho-malarial fever. Such a diagnosis, without a blood examination, is utterly worthless, for unless the parasites of malaria can be demonstrated, we are justified in doubting the diagnosis.

Tuberculosis.—Many cases of tuberculosis exhibit a temperature chart closely resembling that of a quotidian estivo-autumnal infection; but while there may be chills there is no enlargement of the spleen, and examination of the chest will reveal pulmonary lesions not found in malaria. The examination of the blood for the malarial parasites, and of the sputum for the tubercle bacillus, will definitely settle the diagnosis. Not very rarely cases of tuberculosis are observed, complicated by estivo-autumnal fever, especially in the tropics, and here again the microscope is our only aid in making the diagnosis. Such cases are often stumbled upon accidentally while examining the blood of the patients for leucocytosis. (Chart No. 20.)

Hepatic Abscess.—Certain cases of hepatic abscess show an intermittent temperature closely resembling that of estivo-autumnal malaria, and chills are apt to occur. The chief differential clinical points are: In hepatic abscess the liver is enlarged and the spleen is not, as a rule; perspiration is more profuse, and a history of dysentery is obtainable. The examination of the blood will decide, as in malaria the parasites will be present, and the leucocytes decreased, while in hepatic abscess there are no parasites, and there is generally a marked leucocytosis.

Ulcerative Endocarditis.—Certain cases of ulcerative endocarditis resemble quotidian estivo-autumnal fever, in that there are daily rises of temperature, accompanied by chills and sweating. (Chart No. 21.) Examination of the heart will generally suffice to determine the nature of such cases, and if not, an examination of the blood will decide the question.

Yellow Fever.—In regions infested with yellow fever certain pernicious cases of estivo-autumnal malaria are often mistaken for it. This is especially true of the so-called bilious remittent and hemorrhagic forms of pernicious malaria, in which the yellow tint of the skin, the congested eyes, the severe vomiting,

the high temperature, and the occurrence of albumin in the urine, form a clinical picture closely resembling that of yellow fever. In such cases the examination of the blood is most important, and without it the diagnosis of yellow fever is always open to doubt.

Pneumonia, Weil's disease, cholelithiasis, acute suppurative processes in the kidneys, liver, etc., have all been mistaken for attacks of the estivo-autumnal fever.

DIFFERENTIAL DIAGNOSIS OF THE PERNICIOUS FORMS OF ESTIVO-AUTUMNAL FEVER.—In the various pernicious forms of the estivo-autumnal fevers examination of the blood is the one and only method of diagnosis which should be utilized. In these cases we cannot wait for the result of the quinine test, neither can we trust in the clinical symptoms present, for there are numerous other disease processes which so closely resemble in their symptomatology certain forms of pernicious malaria, as to be almost indistinguishable from them. I shall mention the most important:

Cerebral Apoplexy.—The differential diagnosis between cerebral apoplexy and the comatose form of pernicious malaria is often extremely difficult. These cases are accompanied by coma, stertorous breathing, loss of the reflexes, etc., and often simulate cerebral apoplexy very markedly. The main points to be relied upon in arriving at a diagnosis are the high fever, although this is by no means constant, the age of the patient, and the splenic enlargement. An examination of the blood will generally decide the question at once.

Meningitis, bulbar paralysis, acute mania, and tetanus, all of which resemble, in rare instances, certain forms of pernicious malaria, may all be differentiated by a microscopical examination of the blood.

Sunstroke.—In the tropics, and especially among soldiers upon the march, sunstroke closely resembles certain forms of pernicious malaria. It is a well-known fact that in the tropics the heat of the sun seems to excite grave malarial attacks, and this fact should ever be borne in mind in treating cases of so-called sunstroke in these latitudes. The history of previous attacks of malaria, the lack of anemia, the absence of splenic enlargement, and the abrupt onset of the symptoms will aid us in arriving at a diagnosis of sunstroke. In all such cases, however, an examination of the blood should be made, and, if the estivo-autumnal

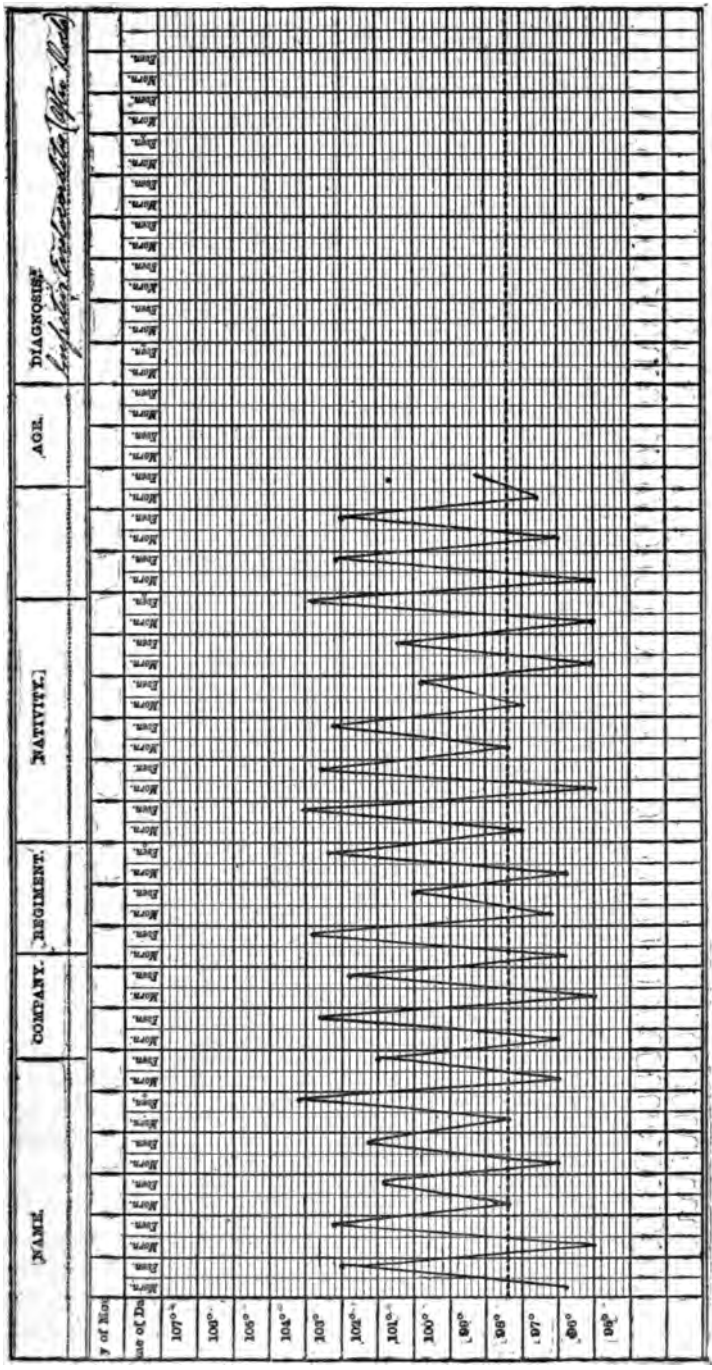


Chart No. 21. Infective Endocarditis. (Deck.)

permitted be found, prompt and energetic treatment with quinine should be instituted.

Among the other disease processes with which pernicious estivo-autumnal malaria may be confounded may be mentioned *cholera*, in which the diagnosis rests entirely upon the results of a blood examination; *dysentery*, in which the diagnosis between the dysentery and the dysenteric form of pernicious malaria must be made, and which can only be done by the microscope; *anemia*, *leukemia*, *pneumonia purpura hæmorrhagica*, and certain nervous diseases, such as *hemiplegia*, *multiple neuritis*, etc.

The diagnosis of the complications attendant upon the estivo-autumnal malarial fevers will not be discussed. In conclusion the examination of the blood has greatly simplified the diagnosis of the malarial fevers, and it can truly be said that he who to-day leaves a patient from malarial fever because of inability to recognize the disease bears upon his shoulders a heavy weight of responsibility, which no regret will lessen.

THE PROGNOSIS OF THE ESTIVO-AUTUMNAL MALARIAL FEVERS

In considering this portion of our subject, I shall discuss the prognosis in each form of estivo-autumnal fever separately, as by so doing we can arrive at a more just conception of the prognosis as it is affected by the occurrence of certain symptoms.

THE QUOTIDIAN ESTIVO-AUTUMNAL FEVER.—The prognosis in cases of quotidian estivo-autumnal fever, provided they are not pernicious in character, and treatment is begun promptly, is always favorable so far as immediate danger to life is concerned. If, however, treatment is not persisted in for several weeks after the symptoms have disappeared relapses almost invariably occur, producing marked anemia and debility, and in such cases the prognosis should be more guarded. Several times I have observed fatal cases of anemia following attacks of this form of malarial fever. In one case the red cells fell to 400,000 per cubic millimeter before death.

In cases which are unrecognized or improperly treated the prognosis is grave. Repeated relapses, together with the complications which may arise, render a favorable prognosis impossible. When complications, such as pneumonia, nephritis, dysentery, etc., accompany the paroxysms, the prognosis is grave, and should be very guarded.

In all the quotidian cases the prognosis given should be influenced by the fact that pernicious symptoms are apt to develop at any time.

THE TERTIAN ESTIVO-AUTUMNAL FEVER.—In uncomplicated cases of tertian estivo-autumnal malaria, properly treated, the prognosis is good. If, however, the patient has suffered from previous attacks, and is greatly debilitated by them, the prognosis is much more grave, as such infections are very often resistant to treatment. This is probably due to diminished absorption of the drug. In cases in which grave complications, such as nephritis and cardiac disease are present, the prognosis should be guarded, and often depends quite largely upon the nature and severity of the complication. The prognosis in the tertian variety of estivo-autumnal malaria is, I believe, better than that of the quotidian form. This I believe because of personal experience, although the Italian observers, from their experience in Italy, claim that the reverse is true.

In untreated cases the prognosis is grave, and the liability of this form to develop pernicious symptoms should always be considered in making a prognosis.

THE PERNICIOUS FORMS OF ESTIVO-AUTUMNAL FEVER.—Pernicious attacks of estivo-autumnal fever may be due to either the quotidian or tertian forms of the parasite, and the prognosis is the same in either case.

The prognosis in the pernicious forms varies with the number of paroxysms and the clinical variety of the fever. If the patient is first seen after having suffered from one or more pernicious paroxysms, the prognosis is very grave, although, if treatment be rigorously instituted, not hopeless. If seen during the first paroxysm the prognosis is grave, and treatment should be at once instituted. In these cases a fatal paroxysm may follow, even after the most energetic treatment.

The Cerebral Pernicious Forms.—The prognosis is most grave in those forms of pernicious malaria which exhibit cerebral symptoms. This is especially true of the comatose form, in which the prognosis is always very grave. A large number of such cases recover with proper treatment, but this form furnishes the greater part of the cases of fatal malarial fever. Untreated, the cerebral forms of pernicious malaria are almost invariably fatal.

The Algid Form.—The prognosis in the algid form is almost

as grave as it is in the cerebral forms, and such cases, if untreated, are generally fatal. Prompt treatment will save many, but not a few go on to a fatal termination despite all treatment.

The Choleraic Form.—The prognosis in this form is also very grave, and Marchiafava and Bignami believe that it ranks next to the cerebral forms in fatality.

The Dysenteric Form.—The prognosis in the dysenteric form of estivo-autumnal fever is grave, and I have observed several cases which resulted fatally in spite of treatment. The prognosis in such cases should depend quite largely upon the severity of the dysenteric symptoms, and the degree of anemia present. The paroxysms are apt to be hidden by the intestinal phenomena, and the malarial element remains long undetected before proper treatment is begun. Death is generally the result of exhaustion and anemia in these cases.

The Pneumonic Form.—In the pneumonic form the prognosis is grave, and, if untreated, a large proportion of the cases result fatally.

The prognosis in the other forms of pernicious malarial fever, as the diaphoretic, cardialgic, and hemorrhagic, is always grave.

IRREGULAR AND CONTINUED FEVERS.—The prognosis in these cases is more grave than in the regularly intermittent estivo-autumnal attacks, but less so than in the pernicious forms.

GENERAL FACTORS INFLUENCING PROGNOSIS.—There are some general factors to be taken into account in making a prognosis in the estivo-autumnal malarial fevers, the chief of which are: location, race, age, occupation, and physical condition of the patient.

1. *Location.*—In certain localities the prognosis is much more grave than in others. In the tropics the prognosis in this class of malarial fevers is much more grave than in temperate regions; and again, in certain regions in the tropics these fevers are much more fatal than in others. For instance, estivo-autumnal malaria is more serious and fatal in Santiago, Cuba, than in Havana, Cuba.

2. *Race.*—The negro enjoys a relative immunity from the estivo-autumnal fevers, and the prognosis is more favorable than in the lighter-skinned races. Koch has conclusively proven that such is the fact.

3. *Age.*—The prognosis is most grave at the extremes of life. In the aged it is always very grave.

4. *Occupation and Position in Life.*—The prognosis in those well-to-do is almost always more favorable than in the poor. This is so, both because the physical condition of the first class is generally better than that of the second, and that, in the first, the disease is at once treated, while in the second it often exists for some time before relief is sought.

The prognosis in the case of soldiers serving in tropical climates is always grave, as has been conclusively proven in the case of our soldiers in Cuba and the Philippine Islands. While intelligent treatment has, in the vast majority of cases, prevented a fatal termination of the acute attack, the debility and anemia occasioned by them have too often proved fatal.

5. *Physical Condition.*—It is obvious that the prognosis is more grave in the cases of individuals in ill health than in those who have been healthy previous to the malarial attack.

PROGNOSIS IN COMPLICATIONS.—The prognosis in cases of estivo-autumnal malaria attended by complications, is that of the fever and the added complication. It is always more grave than in uncomplicated cases. Among the complications which render very grave the prognosis are tuberculosis, pneumonia, the infectious fevers, and sunstroke.

PROGNOSIS OF SEQUELÆ.—As a general rule it may be said that the prognosis of the sequelæ of estivo-autumnal malaria is good, though recovery may be long delayed. The most important of the sequelæ will be considered in detail.

Nervous and Mental Sequelæ.—The prognosis in the various nervous and mental sequelæ is good, and recovery usually occurs within a few weeks or months. Insanity, occurring as a sequelæ of malaria, does not generally persist for more than six months, although there may be impairment of the mental faculties for a long time afterward. Malarial paralyses possess a good prognosis, recovery usually occurring.

Nephritis.—The majority of nephritis occurring with, or following these fevers, are rapidly recovered from, and the prognosis is good. A few cases become chronic, and in rare instances the acute form may terminate fatally.

Post-malarial Anemia.—The prognosis in anemia following these fevers depends entirely upon the character of the anemia. I have already described the forms of anemia occurring after these fevers and will not reconsider them here. Suffice it to say, that the prognosis in the simple secondary anemia is generally

good, the blood regaining its normal number of red cells after weeks or months. This may be the result in cases in which the red cells have been very markedly reduced in number. As a rule, in these cases, the red cells increase rapidly until they number about 2,500,000 per cubic millimeter, after which the increase is very slow.

The prognosis in those cases in which the anemia assumes a pernicious type is always most grave, death usually occurring.

Malarial Cachexia.—In cases in which a change of locality can be effected the prognosis, under suitable treatment, is good, otherwise it is grave.

The following axiom should never be forgotten: The prognosis in all cases of estivo-autumnal malaria is grave, because at any time during their course pernicious symptoms may develop.

While it is comparatively easy to give a prognosis in these fevers of malaria so far as immediate recovery from an attack is concerned, the prognosis as to ultimate cure of the malarial infection should be very guarded. Relapses are sure to occur unless quinine is given for months after the first paroxysm, and very often a change of climate is found absolutely necessary. One of the most discouraging features of the estivo-autumnal variety of malaria is the extreme tenacity of the infection.

CHAPTER XVIII

THE PROPHYLAXIS AND TREATMENT OF THE ESTIVO-AUTUMNAL FEVERS

PROPHYLAXIS

THE subject of prophylaxis in the estivo-autumnal fevers is of very great importance, and in the light of our recently gained knowledge of the transmission of the disease by the mosquito, one which should receive the attention of every physician and sanitarian. Until recently we were ignorant of the source of the malarial poison, and could do but little toward preventing its spread; but now it is not too much to hope that in time the malarial fevers will be as rare as are now some of the acute infectious diseases. Prophylactic measures may be divided into *general* and *personal*, and these will be considered separately.

GENERAL PROPHYLACTIC MEASURES.—We now know that the mosquito not only transmits the disease to man, but acts as an intermediary host of the parasite; it follows, then, that in order to prevent malarial disease the most important general measure is the destruction of the mosquitoes and their larvæ. Many methods have been devised for the latter purpose. We are indebted to L. O. Howard for the most valuable of these, and I shall quote largely from his most valuable study* in the consideration of this portion of our subject.

Regarding the destruction of the larvæ of the mosquito and the abolition of its breeding places he says:

"Altogether the most satisfactory ways of fighting mosquitoes are those which result in the destruction of the larvæ or the abolition of their breeding places. In not every locality are these measures feasible, but in many places there is absolutely no necessity for the mosquito annoyance. The three main preventive measures are the draining of breeding places, the introduction of small fish into fishless breeding places, and the treatment of such pools with kerosene. These are three alternatives,

*"The Mosquitoes of the United States," Bull. 25, Dept. of Agriculture.

any one of which will be efficacious, and any one of which may be used where there are reasons against the trial of the others.

"*Kerosene on Breeding Pools.*—In 1892 the writer published the first account of extensive out-of-doors experiments to determine the actual effect upon the mosquitoes of a thin layer of kerosene upon the surface of water in breeding pools and the relative amount to be used. He showed the quantity of kerosene necessary for a given water surface, and demonstrated further that not only are the larvæ and pupæ thereby destroyed almost immediately, but that the female mosquitoes are not deterred from attempting to oviposit upon the surface of the water, and that they are thus destroyed in large numbers *before their eggs are laid*. He also showed approximately the length of time for which one such treatment would remain operative.

"The quantity of kerosene to be practically used, as shown by the writer's experiments, is approximately one ounce to fifteen square feet of water surface, and ordinarily the application need not be renewed for one month. Since 1892 several demonstrations, on both a large and a small scale, have been made. Two localities were rid of the mosquito plague under the supervision of the writer by the use of kerosene alone. On ponds of any size the quickest and most perfect method of forming a film of kerosene will be to spray the oil over the surface of the water.

"*Drainage.*—The remedy which depends upon draining breeding places needs no extended discussion. Naturally the draining off of the water of pools will prevent mosquitoes from breeding there, and the possibility of such draining and the means by which it may be done will vary with each individual case. The writer is informed that an elaborate bit of work which has been done at Virginia Beach bears on this method. Behind the hotels at this place, the hotels themselves fronting upon the beach, was a large fresh-water lake, which, with its adjoining swamps, was a source of mosquito supply, and it was further feared that it made the neighborhood malarious. Two canals were cut from the lake to the ocean, and by means of machinery the water of the lake was changed from a body of fresh to a body of salt water. Water that is somewhat brackish will support mosquitoes, but water which is purely salt will destroy them.

"*Practical Use of Fish.*—The introduction of fish into fishless breeding places is another matter. It may be undesirable to

treat certain breeding places with kerosene, as, for instance, water which is intended for drinking, although this has been done without harm in tanks where, as is customary, the drinking supply is drawn from the bottom of the tank. An interesting case, noted in "Insect Life" (Vol. IV, p. 223), in which a pair of carp was placed in each of several tanks in the Riviera, is a case in point. The value of most small fishes for the purpose of destroying mosquito larvæ was well indicated by an experience described to us by Mr. C. H. Russell, of Bridgeport, Connecticut. In this case a very high tide broke away a dike and flooded the salt meadows of Stratford, a small town a few miles from Bridgeport. The receding tide left two small lakes, nearly side by side and of the same size. In one lake the tide left a dozen or more small fishes, while the other was fishless. An examination by Mr. Russell in the summer of 1891 showed that while the fishless lake contained tens of thousands of mosquito larvæ, that containing the fish had no larvæ.

"The use of carp for this purpose has been mentioned in the preceding paragraph, but most small fish will answer as well. The writer knows of none that will be better than either of the common little sticklebacks (*Gasterosteus aculeatus* or *Pygosteus pungitius*). They are small, but very active and very voracious.

"During the past few years kerosene has been rather extensively used at many places in an effort to limit the mosquito supply. As already pointed out, there are many places where the source of mosquito supply is definitely limited and easy of treatment, and in such cases, on account of the cheapness of kerosene, it will be the best means of eradication. In other places where communities are surrounded with swamp land, or in the case of extensive sea marshes, kerosene can be practically used in connection with other and more elaborate measures, comprehending, as a rule, dyking and draining."

Celli and Cassigrandi* have investigated very thoroughly the action of various agents upon the mosquito, and their conclusions are as follows:

"(1) Of the whole period of the cycle of development of mosquitoes the stages in which they are most easily destroyed are those of larvæ and of the aerial mosquito, and larvæ are most easily killed the younger they are.

"(2) To kill the larvæ, among numerous substances experi-

*"Annali d'Igiene Sperimentale," Vol. IX, Fasc. III, 1899.

mented with, these will have, in decreasing order, culicidal action:

(a) Mineral: sulphurous oxide, permanganate of potash with hydrochloric acid, common salt, potash, ammonia, carburet of lime, corrosive sublimate, chloride of lime, the bisulphites, sulphate of iron or copper, lime, bichromate of potash, and sodium sulphite. (b) Organic: powders of the unexpanded flowers of chrysanthemum, tobacco, petroleum and oils, formalin, cresol, certain aniline colors (gallot, green malachite), coal tar. Taking into account, however, the dose necessary to kill the larvæ, the practicability and the price, all of the mineral and some of the organic substances are excluded, and there remain as available the vegetable powders, petroleum, and the aniline colors.

"(3) To kill aerial mosquitoes, we have odors, fumes, or gases. Among the odors are turpentine, iodoform, menthol, nutmeg, camphor, garlic. Among the fumes are tobacco, chrysanthemum powder, fresh leaves of eucalyptus, quassia wood, pyrethrum powder. Among the gases, sulphuric oxide. It is, however, to be noted that for these odors, fumes, or gases to exercise their culicidal action they must fill or saturate the whole ambient; otherwise they produce only apparent death, or at most only a culicifugal action, which sometimes in houses may be useful in protecting man from being bitten by mosquitoes, and preventing the latter infecting him when they have sucked the blood of malarious persons.

"(4) The problem of the destruction of mosquitoes is experimentally soluble, but practically it will only be so when economic interests desire it. In this latter sense it is remarkable that the old larvicidal use of petroleum has not become much diffused in those places where it is very cheap. The chrysanthemum plants might be grown on a large scale, this making the malarial place itself produce that substance which frees it of the mosquitoes that infest it.

"(5) The opportune season for killing the larvæ is in the winter, when they are in least numbers in the waters and new generations are not born; this also is the season for their destruction in houses, for they come here for a warmer abode. Their habits and places of nesting should be studied to this end. This may not be accomplished on a large scale as easily as some boast; nevertheless, after the treasures spent by nations and individuals for preserving vines and vegetation from the oidium, the peronospora, and the phylloxera, we may hope that something

may be done for protecting the life of man from the mosquitoes of malaria."

It would seem from the quotations cited that next to abolishing the breeding places of the mosquitoes the use of kerosene is at once the cheapest and most practicable agent of which we have knowledge, at present, for the destruction of the larvæ of the insect. If all stagnant pools and ditches surrounding dwelling-houses in malarious localities were treated once a month with kerosene as recommended by Howard, malarial fever in such localities would be very greatly diminished and perhaps even disappear.

The planting of eucalyptus trees has been urged by numerous observers as a protection against malaria, and while there seems to be some truth in the theory, it has been shown by Nuttall that it is not always successful.

PERSONAL PROPHYLAXIS.—A great deal may be done in the way of personal prophylaxis against malaria by the adoption of certain well-known measures.

If one is obliged to travel in malarious districts, the season of the year in which the malarial fevers are least prevalent should be selected. The use of a mosquito net is most important. It should be the constant companion of the traveler in the tropics, and every night should be passed beneath it. The adoption of the mosquito net by armies operating in malarious regions, especially in the tropics, would undoubtedly do more toward preventing malarial disease than any other sanitary measure. Since the adoption of the mosquito net in the barracks of the United States troops at Camp Columbia, Havana, Cuba, malarial fever has become very rare, whereas it was very common.

In selecting camping sites, or locations for buildings in malarious regions, high, well-drained land should be chosen, and exposure at night, unless protected by the mosquito netting, should be avoided.

Drinking water should always be boiled, for though malaria is but seldom conveyed by it, and then only accidentally, the measure may prevent other diseases which would so deplete the organism as to render it very easily susceptible to the malarial poison. It is advisable to sleep above the ground floor if mosquitoes are numerous, and to have the windows protected by screens and netting. For the protection of the hands and face during the day, or when compelled to travel at night, and mosquito nets cannot be used,

various odorous substances have been successfully used. These are all smeared upon the skin and renewed as needed. Among the most useful are: oil of pennyroyal, camphor, kerosene, oil of eucalyptus, a mixture of oil of tar and sweet oil, as recommended by Nuttall, oil of anise and tar water; the last, which is advocated by Osborne, and quoted by Nuttall, is prepared as follows: "Coal tar is placed in a shallow vessel, and oil of tar or oil of turpentine is added to it and stirred. The vessel is then filled with water and allowed to stand some days until the water is impregnated. The water is used as a wash."

For the protection of houses from mosquitoes the windows should be well screened by fine netting, and kept closed, unless screened, at night. The burning of pyrethrum powders within the house is efficacious.

It is a fact well sustained by practical experience that a most valuable aid in the prophylaxis of malaria, in malarious regions, especially in the tropics, is the daily exhibition of a small dose of quinine, preferably the sulphate, in doses of .10 to .20.

TREATMENT OF THE ESTIVO-AUTUMNAL MALARIAL FEVERS

The treatment of the estivo-autumnal malarial fevers may be divided into hygienic and medicinal, and both should be combined in every case.

HYGIENIC TREATMENT.—Rest is most important, and every case of estivo-autumnal malaria should be confined to bed, so long as there are active symptoms present. While many cases recover without being thus confined, and some without any treatment, it is a good general rule to insist upon absolute rest in these cases. Treatment by quinine is always much more effective if the patient keeps his bed, and recovery is always more rapid and complete. The danger of pernicious symptoms developing in these cases should never be forgotten and should always be guarded against.

Diet.—In all cases the diet should be light during the paroxysms, consisting of milk, soups, soft-boiled eggs, etc. After the acute symptoms are passed a more liberal diet is indicated, and the more nutritious it is the better, as in these cases the debility and anemia which often follow fever is astonishing. The diet should be regulated in accordance with the symptoms present.

The *sick room* should be, if possible, in an upper story, and

well ventilated. The windows should be screened, and every precaution taken to avoid cold drafts.

The patient should be guarded against any irritation, as in many cases of estivo-autumnal malaria the nervous irritability is very great.

A change of climate in cases which have suffered from relapses is often advisable and necessary, and without such a change treatment may be of but little avail.

MEDICINAL TREATMENT.—The medicinal treatment of the estivo-autumnal malarial fevers may be summed up, in the overwhelming majority of cases, in the one word "quinine." In quinine we possess a true specific for all forms of malaria, and disappointment and disgust will follow the use of other drugs, which are from time to time vaunted as equal or superior to quinine. As is well known, cinchona was introduced into Europe in 1640, and immediately gained a well-deserved repute in the treatment of fevers of malarial origin. Its active principle, an alkaloid, is the quinine of to-day, and various salts of the drug are now available. In considering the therapeutic use of quinine or its salts in the estivo-autumnal malarial fevers, the following points should receive our attention:

1. The Action of Quinine upon the Estivo-autumnal Parasite.
2. The Time of Administration.
3. The Form in which it should be Administered.
4. The Methods of Administration.
5. The Amount to be Administered.
6. Contra-indications to its Administration.

1. THE ACTION OF QUININE UPON THE MALARIAL PARASITES.

—The beneficial action which quinine exerts upon the malarial fevers is due to the fact that it is a protoplasmic poison, acting directly upon the malarial parasites. Binz, in 1867, was the first observer to enunciate this theory of the action of quinine, and Golgi, Antolisei, Romanowsky, Mannaberg, Dock, Marchiafava, Celli, Sternberg, and others have proven its truth. All these observers have shown that quinine causes the degeneration of the young malarial parasites, most marked at the time of segmentation. Marchiafava and Bignami have carefully studied the effects of quinine upon the estivo-autumnal parasites, and conclude their observations as follows: "Quinine acts upon the malarial parasites in that phase of their life in which they are nourished and developed. When the nutritive activities cease,

by an arrest of the transformation of hemoglobin into black pigment, and the reproductive phase begins, the quinine is ineffectual in its action."

From personal observations I have noted the following changes in the estivo-autumnal parasites; these changes are confined entirely to the young hyalin and pigmented intracorpuscular forms:

A few hours after the administration of quinine the small hyalin parasites, both quotidian and tertian, have lost their amoeboid motion, and appear more or less contracted or distorted in shape. The perfect "ring-form" is lost, and bizarre shapes are common. The red cell containing the parasite is generally green in color and is very apt to be much crenated. The young pigmented forms appear shrunken, and their protoplasm more granular, while the infected red cell is very dark green in color, shrunken, and crenated.

A study of the staining reactions of the malarial parasites after they have been acted upon by quinine reveals the reason for the morphological changes noted to consist in the degeneration of the vital elements of the organism, brought about by the drug. Romanowsky* has devoted much study to this subject, and has demonstrated that after quinine has been administered the parasites lose their affinity for various stains, this loss being confined almost entirely to the chromatin substance of the nucleus, and that most of the newly formed segments are without a nucleus.

2. TIME OF ADMINISTRATION.—From what has been said it will be seen that quinine is most efficacious if it be present in the blood when segmentation of the parasites occurs, as it acts most energetically upon the newly born parasites. In the regularly intermittent tertian and quartan fevers, as well as in the uncomplicated quotidian and tertian estivo-autumnal fevers, the time of administration can be so arranged as to accomplish this result, but in the pernicious and irregular forms of estivo-autumnal malaria this is impossible.

In the regular quotidian and tertian estivo-autumnal fevers the quinine should be administered in doses of 1.5 to 2, or grs. xx to xxx, four to six hours before the expected paroxysm, or the latter portion of the previous attack.

In pernicious and irregular cases this rule cannot be applied; in the pernicious cases the administration of quinine is indicated

*Cent. für Bak't., 1892, XI., No. 6, 7.

at once, while in the irregular cases a dose of .40 should be given every four hours for several days. The administration of .35 to .40, or grs. v to vi, of quinine, every four hours, I have found to be fully as satisfactory in the treatment of even the regularly intermittent estivo-autumnal fevers, as the single large dose first mentioned, and the interrupted method of administration is the one which I personally prefer. The results obtained are as good, and the discomfort to the patient is, as a rule, much less. Dock,* in a most valuable paper, concludes in favor of the administration of large doses, three to six hours before the expected paroxysm. Theoretically, this is absolutely correct, and should always be followed in the regularly intermittent malarial fevers of benign tertian and quartan causation; but in the estivo-autumnal fevers the results obtained are no better, in my experience, than those in which the numerous smaller doses have been given. It should also be remembered that many patients are unable to absorb but a small quantity of quinine at a time, and in such cases the greater part of a large dose would be simply wasted. I am convinced that many of the most resistant cases of estivo-autumnal malaria depend upon the inability of the patient to absorb the quinine which is administered. There are certain cases, however, which do not respond to small doses of quinine, often repeated, but which recover rapidly under large doses.

As in the treatment of all diseases, each case should be judged individually, and treated accordingly.

In all cases which exhibit pernicious symptoms, the quinine should be administered at once.

3. THE FORM OF QUININE TO BE ADMINISTERED. — There are ten salts of quinine which are, or have been used, in the treatment of estivo-autumnal malaria, but of these there are but two which merit general use. These are the sulphate and the dihydrochlorate or bimuriate of quinine. The sulphate contains 74.31 per cent of quinine, while the bimuriate contains 81.61 per cent. The first is soluble in the proportion of one part to nine parts of water, while the latter is soluble in the proportion of one part to .96 parts of water.

From this it will be seen that the bimuriate of quinine is to be preferred theoretically, but practically, on account of its cheapness, the sulphate is most useful.

In cases in which the hypodermic or intravenous use of the

* "Quinine in Malaria," Jour. Am. Med. Association, July 29, 1900.

drug is indicated, the hydrochlorate (the bimuriate) should always be used.

4. METHODS OF ADMINISTRATION OF QUININE.—Quinine may be administered in three ways, i. e., by the mouth, hypodermically, and intravenously. In rare instances it has been administered by the rectum, but this method is undeserving of consideration, as it is unsatisfactory and unnecessary.

Administration by the Mouth.—In the great majority of cases quinine is administered by the mouth. The form of salt used is generally the sulphate, in the form of solutions, capsules, pills, or tablets. This method of administration is the most satisfactory in the great majority of cases, and, save in rare instances, can be resorted to. When possible, the quinine should be given in solution, a drop of dilute hydrochloric or sulphuric acid being added for every grain (.065) of the drug. To disguise the horribly bitter taste which the solution has, the syrup of yerba santa is most efficient. Many cases, however, refuse to take the quinine in solution, and in such instances capsules, pills, or tablets may be used. Of these the gelatin capsules are much to be preferred, as they are quickly soluble. Tablets are generally to be preferred to pills, which are too often extremely insoluble.

Personally I use quinine in solution or in capsules, in administering the drug by the mouth.

Administration by the Hypodermic Syringe.—In cases of estivo-autumnal malaria, in which the symptoms are of pernicious character, and, again, in cases which cannot take quinine by the mouth, the hypodermic use of the drug is indicated. In pernicious cases it should be resorted to without delay, as it is necessary to bring the drug in contact with the parasites as soon as possible.

The solution which is generally used is the following:

℞ Hydrochlorate of quinine 5. (grs. lxxv).
Distilled water q. s. add 10. (z jiss).

In this solution 1 c.c. (15m) contains .5 (grs. vjiss) of quinine.

Extreme care should be used in making the injection, as induration and even abscess formation is apt to follow the administration of the drug in this manner. The syringe should be sterilized thoroughly, and also the skin over the area in which the injection is to be made; the solution should be perfectly clear

and freshly prepared; the abdomen, back, or gluteal region may be selected, but the gluteal region is preferable; the injection should be made into the muscles, therefore the needle of the syringe should be deeply inserted; the wound made by the needle should be covered with a thin coating of collodion.

Much discomfort and pain generally follows the injection of quinine into the subcutaneous tissues, and if the operation is carelessly done, no precautions as to cleanliness being observed, severe necrosis of the skin and abscess-formation may occur. If aseptic precautions are observed, however, these may almost invariably be avoided, although more or less induration around the site of injection is of common occurrence.

Intravenous Injection of Quinine.—To Baccelli we owe this method of administering quinine. It is indicated whenever the most prompt effect of the drug is required, as in pernicious cases after one paroxysm has been succeeded by another, or the patient's strength is rapidly failing, or when other treatment has proved unavailing. Marchiafava and Bignami urge this method, especially in the algid forms of pernicious estivo-autumnal fever.

Baccelli's solution is as follows:

R Hydrochlorate of quinine	1.	(grs. xv).
Chloride of sodium	.75	(grs. xji).
Distilled water q. s. add	10.	(z ijs).

The whole amount is to be injected and the solution should be perfectly clear and tepid.

The method of injecting is thus described by Baccelli*: "After the veins of the forearm have been made turgescient by means of a circular tourniquet, we introduce a Pravaz needle from below upward into the lumen of the vein. We select a small one, in order to avoid hemorrhage afterward. The syringe holds 5 centimeters and is filled according to the dose which is to be given, and connected with the needle before its introduction."

It is, of course, very important that all the precautions as regards cleanliness should be observed here as in the hypodermic injection of the drug.

5. THE AMOUNT OF QUININE TO BE ADMINISTERED.—There is no doubt but that we err more often upon the side of excess in administering quinine than vice versa. It is not uncommon to

* "Za Riforma Medica," January, 1890.

observe the use of from 5 to 6 grams of the drug during the twenty-four hours, even in the mild intermittent fevers. Such large doses are simply criminal, for they occasion much harm to the system. From personal experience I believe that 2 grams, or 30 grains, of quinine in the twenty-four hours is amply sufficient to cure any case of ordinary estivo-autumnal malaria, if it is properly administered. I have never seen a case in which treatment was begun in time which did not succumb to that amount of the drug, and I have seen many cases recover rapidly when but 1.3 grams, or xx grains, were administered during the twenty-four hours.

When the drug is used hypodermically a dose of .5 grams, or $7\frac{1}{2}$ grains, should be administered, and repeated, if necessary, until about 1.3 grams (grains xx) have been injected. Some very severe cases may require more than the above amount, but they will be rare, and will probably prove fatal in any event.

When given intravenously the dose which Baccelli recommends is one gram.

Stated briefly, the amount of quinine to be used in the treatment of estivo-autumnal malaria is as follows: By the mouth, 1.3 to 2.5 grams (grains xx to xxxv); hypodermically, .65 to 1.3 grams (grains x to xx); intravenously, 1 gram (grains xvi).

As soon as the active symptoms of the paroxysm have subsided, the dose of the quinine which has proven efficacious may be gradually diminished, but the drug should be used for several weeks afterwards.

An ordinary case of either quotidian or tertian estivo-autumnal malarial fever should be treated, then, as follows: The patient should, if possible, keep his bed. The bowels should be thoroughly opened by calomel, .32 grams (grains v), and the diet should be light and nourishing. Quinine, .32 or grains v, should be given every four hours until after the active symptoms of the fever have disappeared, and every five hours for a period of three days following. For the next week quinine in doses of one gram (grains xvi), on every other day should be administered, and for a period of at least three months afterwards, a dose of quinine of 1.3 grams (grains xx), should be taken every sixth day. If this treatment is followed out a cure of the disease will be reasonably sure.

One of the most serious mistakes which is made in the treat-

ment of estivo-autumnal malaria is the too early abandonment of quinine. These infections are very resistant, and relapses are almost sure to occur unless quinine is administered for weeks after the patient is apparently well.

6. CONTRAINDICATIONS TO THE ADMINISTRATION OF QUININE.—There are certain individuals, few in number, who undoubtedly are unable to take quinine. In all, the use of large doses of this drug produce unpleasant symptoms, such as tinnitus aurium, vertigo, confusion of thought, etc., but in certain individuals symptoms occur which may even endanger life, or, at least cause such suffering as to render the administration of the drug inadvisable. Among such symptoms may be mentioned amaurosis, which may be persistent, deafness, dyspnoea, cardiac weakness, severe cutaneous eruptions, metrorrhagia, hemorrhage from the bowels, hematuria, and even fatal collapse.

Patients who suffer from these unusual symptoms, which are really due to the poisonous effect of quinine, even in therapeutic doses, upon them, are generally aware of their idiosyncrasy in this respect and refuse to allow it to be given, and, indeed, the appearance of such symptoms are contraindications to the use of the drug. In such cases some substitute for quinine must be used, and the most important of these will now be considered, always remembering that there is *no substitute* for quinine when it can be borne.

SUBSTITUTES FOR QUININE.—Among the alkaloids besides quinine which have been separated from the cinchona bark are quinidine, cinchonidin, and cinchonine, all of which have been used successfully in place of quinine.

Euchinin.—This is a new tasteless product, an ethyl carbonate of quinine. It has many of the bad effects of quinine, as deafness and derangement of vision, and it has to be given in larger doses. St. George Gray, Mori, Lewkowitz, and Goniev have used it in many cases of malarial fever, and claim that it is a valuable addition to our therapeutic resources. The dose is a little less than twice that of quinine. Personally I have had no experience with this drug.

Methylene Blue.—The use of this drug in malarial fever was first advocated by Guttman and Ehrlich, whose attention was drawn to it by the observations of Celli and Guarneri, that by its use the malarial parasite could be stained while living. In isolated cases it undoubtedly effects a cure, but it is much less

effective than quinine. Marchiafava and Bignami think that it is worse than useless, as it may produce strangury, diarrhea, and temporary albuminuria. Thayer regards its use favorably, but has found that the malarial parasites acquire a seeming tolerance to it. From personal observations I am convinced that sometimes it effects a cure, but that it is very much less valuable than quinine. The dose is from .5 grams (grains viii) to .1 gram (grains xvi) in the twenty-four hours.

The urine is colored blue by it, and it is always well to warn the patient of this fact.

Phenocoll.—The hydrochlorate of phenocoll, a derivative of phenacetin, has been investigated by numerous observers, notably Albertoni, Pucci, Novi, Anconi, and F. Plehn. The general consensus of opinion is that, while it is sometimes useful in the mild tertian and quartan fevers, it is of but little use in the treatment of the estivo-autumnal infections; while it is not free from injurious effects, as symptoms of collapse have followed its use. The dose is from 1 to 3 grams (grains xvi to lv) during the twenty-four hours.

Lemons.—Tomassi-Crudelli has observed a marked improvement in old malarial infections from the use of lemon juice and decoction of the lemon.

From this brief summary of the drugs which are used as substitutes for quinine, it will be observed that they are few in number, and that none of them can be ranked with quinine, which is the true specific for all malarial diseases.

TREATMENT OF SPECIAL SYMPTOMS AND COMPLICATIONS.—There can be no doubt that a cathartic dose of calomel enhances the effect of quinine, and it should always be used even in those cases presenting intestinal symptoms.

The *vomiting* if exhausting may be controlled by hypodermic injections of morphine.

The *headache* is best relieved by cold applications, and if there is great nervous excitement or delirium, morphine is indicated. The symptoms occurring during pernicious attacks should receive proper treatment. High temperature, if it shows no signs of declining, should be treated with tepid baths; cardiac weakness, by suitable stimulants; algid symptoms should be treated by stimulants, massage, and heat applied by means of hot-water bottles and warmed blankets; collapse should be treated by hypodermic injections of brandy, strychnine, ether, and by transfusion.

Complications.—The complications should be appropriately treated, the malarial infection being promptly conquered by quinine.

TREATMENT DURING CONVALESCENCE.—During convalescence, besides the administration of quinine in the manner indicated, the use of some form of iron is advisable, on account of the marked anemia which is usually present. Bland's pill is a very valuable therapeutic aid in these cases. In cases which show a profound degree of anemia, and which do not improve with iron alone, arsenic should be given in the form of Fowler's solution, and administered in gradually increasing doses.

The diet should be generous and nutritious, sufficient outdoor exercise should be insisted upon, and precautions taken to avoid reinfection.

In all cases where it is possible, a change of climate to a high, dry altitude, known to be non-malarious, should be urged. This will do more for the patient than any other therapeutic measure. Bitter tonics are often very useful, and the use of some good mineral water is indicated.

The above remarks apply as well in the treatment of chronic malaria cachexia as in convalescence from acute attacks.

The treatment of the sequelæ of the estivo-autumnal malarial fevers will not be considered here, as it differs in no way from that ordinarily pursued in the diseases themselves, save that the malarial element should always be remembered and acute attacks guarded against.

INDEX

- Abscess, hepatic, diagnosis from, 191.
- Age, as predisposing cause of, 61.
in prognosis, 196.
- Air, direct infection by, 62.
- Albuminuria, as a sequela of, 88, 179.
- Algid form, prognosis of, 195.
symptoms of, 152.
- Altitude, as predisposing cause, 59.
- Amaurosis, as a sequela, 182.
- Anæmia, 82.
post malarial, 85, 182.
pernicious, as a sequela, 183, 197.
prognosis of, 197.
- Anopheles claviger, 35, 68.
pictus, 35.
nigripes, 35.
- Anopheles, methods of distinguishing, 35, 39.
- Aphasia, as a sequela, 178.
- Arteritis, as a sequela, 179.

- Bacteria in malaria, 5.
- Blood, examination of, 16, 22, 48, 166, 185.
examination of during clinical periods, 19, 21, 119.
methods of staining of, 50.
objects mistaken for parasites in, 49.
general pathology of, 79.
- Bone marrow, changes in, 98.
- Brain, 92.
blood-vessels of, 92.
changes in nerve cells of, 93.
endothelial cells in, 93.
free parasites in, 93.
free pigment in, 93.
macrophages in, 93.
pathology of, 92.
pigmented leucocytes in, 93.
segmentation in, 92.
- Bronchitis, acute, complicating, 109.

- Cachexia, 88, 183, 198.
prognosis of, 184, 198.
as a sequela, 183.
treatment of, 213.
- Camp, choice of, 203.

- Cadaver, appearance of, 92.
- Cardiac weakness, treatment of, 212.
- Cardialgic form, prognosis of, 154.
- Cells, endothelial, phagocytic action of, 43.
splenic pulp, 43.
bone marrow, 43.
- Chills in estivo-autumnal malaria, 110.
- Cholera, differential diagnosis from, 194.
- Choleraic form, 153.
prognosis of, 196.
- Chromatin, staining reactions of, 54.
- Climate, influence of, 59.
- Classification, 45.
morphological, 45.
clinical, 104.
- Collapse, treatment of, 212.
- Complications, 168.
circulatory system, 170.
digestive system, 171.
genito-urinary system, 170.
excretory system, 170.
nervous system, 168.
respiratory system, 168.
- Convalescence, change of climate during, 213.
diet during, 213.
treatment during, 213.
- Corpuscles, red blood, 8, 9.
color of, 8, 9.
shape of, 8, 9.
destruction of, 79, 82.
hemoglobin in, 79, 84.
number of parasites in, 8.
parasites in, 8, 9.
reduction of, 82.
- Corpuscles, white, reduction of, 84.
- Countries, malarial, 58.
- Crescents, degeneration of, 10.
development of flagellated form from, 29.
development of, in mosquito, 37.
discovery of, 6.
distinction between tertian and quotidian, 25.
fertilization of, 31.

- Crescents, fragmentation of, 26.
 in the bone marrow, 98.
 in the spleen, 97.
 nature of, 32.
 origin of, 32.
 outline of, 9, 24.
 pigment in, 9, 24.
 protoplasm of, 24.
 quotidian, 25.
 significance of, 32.
 staining reactions of, 55.
 tertian, 25.
 time of occurrence of, 24.
 vacuolization of, 25.
 Cultivation experiments, 40.
 Cycle of the estivo-autumnal parasites, 11.

 Daytime as predisposing cause, 59.
 Deafness, as a sequela, 182.
 Diaphoretic form, symptoms of, 155.
 prognosis of, 196.
 Diagnosis, of the quotidian form, 186.
 of the tertian form, 186.
 of pernicious forms, 186.
 of irregular and continued forms, 187.
 by examination of the blood, 51, 185.
 Diagnosis, differential, from typhoid, 188.
 from tuberculosis, 191.
 from hepatic abscess, 191.
 from ulcerative endocarditis, 191.
 from yellow fever, 191.
 from cholera, 194.
 from dysentery, 194.
 from uræmia, 194.
 from leukæmia, 194.
 from purpura hæmorrhagica, 194.
 from hemiplegia, 194.
 from multiple neuritis, 194.
 Diet during treatment, 204.
 Digestive system, diseases of as sequela, 179.
 diseases of, as complications, 171.
 Distribution of estivo-autumnal fevers, 58.
 Drapanidium, 45.
 Dysenteric forms, prognosis of, 196.
 symptoms of, 155.
 Dysentery, as a complication, 171.

 Endocarditis, as a sequela, 179.
 as a complication, 170.
 ulcerative, differential diagnosis from, 191.
 Enteritis, as a complication, 171.
 ulcerative, as a sequela, 179.

 Erysipelas, as a complication, 175.
 Etiology, 58.
 Euchinin, 211.

 Facial appearance, 107, 115.
 Fever, definition of estivo-autumnal, 4.
 cause of variations in, 12, 111.
 continuous, 161.
 crisis of, 107.
 effect of quinine on, 121.
 etiology of, 88.
 incubation of, 71.
 latent or masked, 159.
 modifications of, 11, 111, 162.
 pseudocrisis of, 108.
 quotidian estivo-autumnal, 11, 108, 112, 121.
 remittent, 161.
 subcontinued, 161.
 temperature curve of, 11, 108, 112.
 tertian estivo-autumnal, 12, 106, 132.
 variations in, 12, 111.
 Flagella, size of, 28.
 action of, 28.
 pigment in, 28.
 fragmentation of, 29.
 Flagellate bodies, 6, 10, 26.
 activity of, 28.
 active form of, 27.
 pigment in, 27.
 degeneration of, 15, 29.
 development of active form of, 27, 29.
 varieties of, 26.
 methods of obtaining, 26.
 origin of, 26, 33.
 passive form of, 30.
 pigment in passive form of, 30.
 significance of, 31-33.
 sexual nature of, 31, 33.
 staining reactions of, 56.
 Fusiform bodies, 26.

 Gametes, 37.
 Micro, 37.
 Macro, 37.
 Gametocytes, Micro, 37.
 Gastritis as a complication, 171.
 Gastro-intestinal tract, diseases of, complicating, 171.
 diseases of, as sequelæ, 179.
 Genito-urinary system, diseases of, as complications, 170.
 diseases of, as sequelæ, 179.

- Glycosuria as a sequela, 181.
 Gymnosporidia, 45.
- Hæmamoeba malaris*, 6.
 immaculata, 45.
 præcox, 45.
 selicta, 45.
 sub-immaculata, 45.
 sub-præcox, 45.
 vivax, 45.
- Hæmoproteus*, 45.
Hæmosporidia, 45.
Hæmorrhagic form, prognosis of, 196.
- Hæmosiderin*, 81.
 chemical nature of, 82.
 distribution of, 82.
- Halteridium*, 45.
- Headache, treatment of, 212.
- Heart, pathology of, 95.
- Hemiplegia as a complication, 151.
 differential diagnosis from, 191.
- Hemoglobin, retraction of, 49, 79.
 reduction of, 84.
- Hepatic abscess, differential diagnosis from, 191.
- Hepatitis as a sequela, 181.
- Historical, 4.
- Hyaline bodies, discovery of, 6.
 quotidian, 17, 123.
 size of quotidian, 17, 123.
 shape of quotidian, 17, 123.
 activity of quotidian, 17, 123.
 number in the infected corpuscle of, 18, 123.
 tertian, 20, 136.
 size of tertian, 20, 136.
 shape of tertian, 20, 136.
 staining reactions of, 53.
 activity of tertian, 20, 136.
 number in the infected corpuscle of, 20, 136.
- Hysteria as a complication, 151.
- Immunity, 74.
 acquired, 75.
 congenital, 75.
 racial, 75.
- Incubation, period of, 71.
- Infection, combined, 16.
 by air, 62.
 by water, 62.
 by inoculation, 63.
- Inflammation, phlegmonous, as a complication, 175.
- Inoculation, direct infection by, 41, 63.
 experiments in, 41, 63.
 the mosquito and inoculation, 63.
 transmission from man to man by, 41.
- Insanity, as a sequela, 178.
- Insolation, as a complication, 175.
- Iritis, as a complication, 182.
- Keratitis, as a sequela, 182.
- Kerosene, as a prophylactic, 200.
- Kidneys, pathology of, 97.
- Latent or masked fever, 159.
- Laverania malaris*, 45.
 ranarum, 45.
 Danilewski, 45.
- Lemons, as a substitute for quinine, 212.
- Leucocytes, 84, 93.
 decrease of, 84.
 increase of, 84.
 pigment in, 42.
- Leucocytosis, 84.
 apparent, 84.
 real, 84.
- Leukæmia, differential diagnosis from, 194.
- Liver, pathology of, 95.
 cirrhosis of, 181.
- Locality, as a predisposing cause, 58.
- Locality in prognosis, 196.
- Lungs, pathology of, 94.
- Macrophages, 43, 93.
- Malaria, Classification of, 3, 104.
 pernicious forms of, 147.
 quartan, 7.
 quotidian, estivo-autumnal, 15, 22, 108, 121.
 tertian, 7.
 tertian estivo-autumnal, 15, 22, 106, 108, 132.
- Mania as a complication, 168.
- Mania as a sequela, 178.
- Masked or latent fever, 159.
 medicinal treatment of, 205.
- Melancholia as a sequela, 178.
- Melanæmia, 80.
- Melanin, chemical nature of, 81.
 distribution of, 81.
- Meningitis as a complication of, 168.
- Mental sequelæ, prognosis of, 197.
- Methylene blue as a substitute for quinine, 211.
- Mosquito theory, 18, 19, 35, 63.
 evidence in favor of, 63.

- Mosquito experimental evidence of, infection by, 65.
historical, 36.
- Mosquitoes, conditions affording protection from, 199, 203.
development of parasites within, 37, 68.
differentiation of, 39.
methods of study of, 35.
situation of parasite within, 37, 68.
types of, 35.
- Moisture as a predisposing cause, 60.
- Nausea, 112, 212.
- Nephritis, as a complication, 170.
as a sequela, 180.
prognosis of, 197.
- Nervous system, diseases of, as complications, 151.
diseases of, as sequelae, 178.
symptoms connected with, 118.
- Neuralgia, as a sequela, 178.
- Neuritis, multiple, as a sequela, 178.
differential diagnosis from, 194.
- Occupation as a predisposing cause, 61.
- Occupation in prognosis, 197.
- Optic neuritis, as a sequela, 182.
- Orchitis, as a complication, 170.
- Oscillaria malarie, 45.
- Otalgia, as a sequela, 182.
- Ovoid bodies, in brain, 93.
in spleen, 96.
development of, 26.
discovery of, 6.
origin of, 26, 32.
quotidian, 26.
significance of, 32.
staining reactions of, 55.
tertian, 26.
time of occurrence of, 24.
- Paralysis as a sequela, 178.
- Paraplegia as a complication, 168.
- Parasites, in estivo-autumnal fever, 6, 7, 17, 123, 136.
action of quinine on, 205.
amoeboid movements of, 18, 123, 136.
classification of, 11, 17, 45.
crescent forms of, 7, 24, 55.
cultivation of, 40.
description of, 6, 7, 17, 123, 136.
development of in mosquito, 35, 68.
diagnostic value of, 4.
discovery of, 6.
- Parasites, flagellated forms of, 6, 26, 56.
ring forms of, 7, 17, 20, 53, 123, 136.
intracorpuseular, 7, 17, 123, 136.
inoculation of, 41.
methods of staining of, 50.
ovoid forms of, 6, 24, 26, 55.
varieties of, 6, 7.
pigmented forms of, 8, 18, 21, 54.
protoplasm in, 17, 20, 123, 136.
segmenting forms of, 8, 18, 21, 123, 136.
study of, in blood, 19, 22, 48.
- Quotidian estivo-autumnal parasite, 11, 123.
amoeboid movement of, 17, 123.
crescentic form of, 25, 123.
cultivation of, 40.
effect of quinine on, 205.
flagellate forms of, 26.
hyaline form of, 17, 123.
life cycle of, 16, 31, 34, 38.
ovoid forms of, 24.
pigmented forms of, 16, 123.
relation to paroxysm, 19, 119.
shape of, 17, 123.
size of, 17, 123.
segmentation of, 18, 123.
structure of, 17, 123.
- Tertian estivo-autumnal parasite, 20, 136, 146.
amoeboid movement of, 20, 136.
crescentic forms of, 25, 136.
effect of quinine on, 205.
flagellate forms of, 26.
hyaline form of, 20, 136.
life cycle of, 16, 31, 34, 38.
ovoid forms of, 24.
pigmented forms of, 21, 136.
relation to paroxysm, 21, 119.
shape of, 20, 136.
size of, 20, 136.
segmenting forms of, 21, 136.
differential diagnosis, 23, 45.
- Paraplegia as a complication, 168.
- Parotitis as a complication, 175.
- Pathology, general, 79.
special, 91.
- Pernicious estivo-autumnal malaria, 147.
the algid form, 152.
the ataxic form, 152.
the bilious form, 156.
bulbar paralysis in, 152
cause of, 149.
classification of, 148.
comatose form, 149.

- Pernicious estivo-autumnal malaria—**
 cardialgic form, 154.
 choleraic form, 153.
 differential diagnosis of, 192.
 examination of blood in, 157
 the delirious form, 151.
 the diaphoretic form, 155.
 the dysenteric form, 155.
 the eclamptic form, 151.
 examination of the blood in, 142.
 the gastralgic form, 154.
 the hæmorrhagic form, 155.
 parasites in, 147.
 the pneumonic form, 155.
 the syncopal form, 156.
 treatment of, 208.
- Phagocytes, 42.**
 degeneration of, 43.
 substances taken up by, 44.
 varieties of, 43.
- Phagocytosis, action of quinine upon, 44.**
 significance of, 44.
 time of occurrence of, 43.
- Phenocoll, 212.**
- Pigment, yellow, 81.**
 distribution of, 82.
 black, 81.
- Pigmented bodies, quotidian, 18, 123.**
 tertian, 21, 136.
 staining reactions of, 54.
- Pleurisy, as a complication, 170.**
- Polyuria, as a sequela of, 181.**
- Pneumonia, as a complication, 169.**
- Prognosis, 194.**
 in algid form, 195.
 in cardialgic form, 196.
 in choleraic form, 196.
 in diaphoretic form, 196.
 in dysenteric form, 196.
 in hæmorrhagic form, 196.
 in comatose form, 195.
 effect of age upon, 196.
 effect of location upon, 196.
 effect of occupation upon, 197.
 effect of race upon, 196.
 effect of physical condition upon, 197.
 factors influencing, 196.
 in complications, 197.
 in malarial cachexia, 198.
 of nephritis, 197.
 of nervous sequelæ, 197.
 of sequelæ, 197.
 of pernicious forms, 195.
 of pernicious cerebral forms, 195.
 of post malarial anemia, 196.
- Prognosis—**
 of pneumonic form, 196.
 of quotidian type, 194.
 of tertian type, 195.
- Predisposition, altitude in, 59.**
 age in, 61.
 climate in, 59.
 locality in, 58.
 moisture in, 60.
 occupation in, 61
 race in, 61.
 rain in, 60.
 sex in, 61.
 soil in, 60.
 time of day in, 59.
 winds in, 60.
- Prophylaxis, choice of camp in, 203.**
 drinking water in, 203.
 general, 199.
 personal, 203.
 use of kerosene in, 200.
 use of mosquito nets and screens in, 203.
 destruction of mosquitoes in, 199.
 use of odorous principles in, 204.
 use of quinine in, 204.
- Proteosoma, 45.**
- Quartan malaria, parasite of, 7.**
- Quinine as a prophylactic, 204.**
 as a test for malaria, 4.
 contra-indications to use of, 211.
 effect upon parasites of, 205.
 form of, to be administered, 207.
 method of administration of, 208.
 influence on temperature curve of, 12, 15, 16, 121.
 salts of, 207.
 time of administration of, 206.
 substitutes for, 211.
- Quotidian estivo-autumnal fever, 108, 121.**
 afebrile stage of, 112.
 bone marrow in, 98.
 brain in, 92.
 clinical description of, 108, 121.
 chill in, 112.
 distribution of, 58, 104.
 heart in, 95, 116.
 kidneys in, 97, 118.
 liver in, 95, 118.
 lungs in, 94, 116.
 mouth and tongue in, 115.
 paroxysms in, 108.
 phagocytosis in, 44.
 prodromal symptoms of, 108.

- Quotidian estivo-autumnal fever**
 prognosis of, 194.
 remittent fever of, 112.
 retina in, 94.
 skin in, 115.
 spleen in, 96, 116.
 symptomatology of, 108.
 stomach and intestines in, 95, 116.
 temperature curve of, 108.
 time of occurrence of, 104.
 urine in, 86, 118.
- Race as a predisposing cause**, 61.
Race in prognosis, 196.
Rain as a predisposing cause, 60.
Recovery, spontaneous, 76.
 cause of, 76.
Remittent estivo-autumnal fever, 161.
Respiratory system, symptoms connected with, 116.
 complications connected with, 151.
Retina, changes in, 94.
Retinitis as a sequela, 182.
Rheumatism as a complication, 175.
Rhizopoda, 45.
- Sclerica, as a complication**, 175.
Season, the malarial, 64, 104.
Segments, size of, 18, 21, 123, 136.
 staining reactions of, 54.
Segmentation, 18, 21.
 activity of pigment in, 18, 21.
 appearance of pigment in, 18, 21.
 description of parasites in, 18, 21.
 frequency of, in blood, 18, 21.
 in spleen, 18, 21.
 of quotidian parasite, 18.
 of tertian parasites, 21.
 occurrence of, in corpuscles, 18, 21, 123, 136.
 relation of, to paroxysm, 7.
Sequelæ, 175.
 nervous system, 178.
 circulatory system, 179.
 digestive system, 179.
 genito-urinary system, 179.
 glandular system, 181.
 organs of sense, 182.
 treatment of, 213.
- Sex, as a predisposing cause**, 61.
Soil, as a predisposing cause, 60.
Spleen, changes in, 96.
 abscess of, as a sequela, 182.
 crescent forms in, 8, 97.
 enlargement of, 96, 181.
- Spleen, floating**, 181.
 pathology of, 96.
 puncture of, 16.
 rupture of, 181.
- Spores in etiology of malaria**, 5.
Sporozoa, 6, 45.
Sporozoites, 38.
- Staining**, 51.
 methods of, 50.
 Chensinsky's method of, 51.
 Fletcher's method of, 52.
 Laveran's method of, 52.
 Nocht-Romanowsky's method of, 57.
 Romanowsky's method of, 50.
- Stomach, pathology of**, 95.
Sweating, 115.
Symptomatology, 108.
- Temperature curve of, in tertian form**, 11, 15, 108.
 curve of, in quotidian form, 11, 15, 112.
 analysis of, 11, 15, 108, 112.
 irregular, 12, 15, 109.
 parasites, in relation to, 22.
 remittent form of, 114, 161.
- Tertian estivo-autumnal fever**, 106, 132.
 febrile stage of, 108.
 brain in, 92, 118.
 bone marrow in, 98.
 clinical description of, 108, 132.
 distribution of, 164.
 febrile stage of, 108.
 frequency of, 105.
 heart in, 95, 116.
 kidneys in, 97, 118.
 liver in, 95, 118.
 lungs in, 94, 116.
 mouth and tongue in, 115.
 paroxysm of, 107.
 prodromal symptoms of, 107.
 prognosis of, 195.
 remittent fever of, 111.
 stage of remission of, 108.
 stomach and intestines in, 95, 116.
 skin in, 115.
 sweating in, 115.
 symptomatology of, 107.
 temperature curve of, 11, 15, 108.
 time of occurrence of, 104.
 urine in, 86, 118.
- Tonsillitis, as a complication**, 175.
- Treatment**, 204.
 change of climate during, 205.
 diet during, 204.

- Treatment—**
 of convalescence, 213.
 hygienic, 204.
 medicinal, 205.
 of algid symptoms, 212.
 of cardiac weakness, 212.
 of collapse, 212.
 of complications, 213.
 of headache, 212.
 of high temperature, 212.
 of pernicious attacks, 208.
 of sequelæ, 213.
 of vomiting, 213.
 quinine in, 205.
 of special symptoms and complications, 212.
- Tropics, in relation to malaria, 3, 59, 104.**
- Tuberculosis, as a complication, 169.**
 differential diagnosis of, 191.
- Typhoid, as a complication, 171.**
 differential diagnosis from, 188.
 combined infection with, 171.
- Urinary system, symptoms connected with, 118.**
- Urine, 86.**
 acidity of, 87.
 albumin in, 88.
 amount of, 86.
 chlorides in, 87.
 color of, 87.
 indican in, 88.
 iron in, 88.
 sodium and potassium in, 88.
 specific gravity of, 87.
 solids in, 87.
 urea in, 87.
 uric acid in, 87.
- Vacuoles, 49.**
- Variola, as a complication, 175.**
- Vertigo, as a sequela, 182.**
- Vegetable cells in, 5.**
- Viscera, pathological changes in, 91.**
- Vomiting, 116.**
 treatment of, 212.
- Water, direct infection by, 62.**
 boiling of, 203.
- Winds as a predisposing cause, 60.**
- Yellow fever, differential diagnosis of, 191.**

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